



10-04-07

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Attorney Docket No. PC10925A
Express Mail No. EF321670551US

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By

(Signature of person mailing)
Christian Smolizza

(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE: U.S. PATENT NO. 6,667,314
ISSUED: DECEMBER 23, 2003
TO: MANOUSSOS PERROS, DAVID ANTHONY
PRICE, BLANDA LUZIA CHRISTA STAMMEN and
ANTHONY WOOD
FOR: TROPANE DERIVATIVES USEFUL IN THERAPY
FROM: SERIAL NO. 09/865,950
OF: MAY 25, 2001

Commissioner for Patents
Mail Stop Patent Extension
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

**TRANSMITTAL OF REQUEST FOR EXTENSION OF
PATENT TERM UNDER 35 U.S.C. §156**

Transmitted herewith are the application papers of PFIZER INC., dated October 3, 2007 for extension of the term of U.S. Patent No. 6,667,314 under 35 U.S.C. §156, based on the regulatory review period for SELEZENTRYTM (maraviroc) Tablets, together with two duplicate copies as required under 37 C.F.R. §1.740(b) and two additional duplicate copies of the application pursuant to M.P.E.P. §2753, for a total of four copies and one original.

As set forth under 37 C.F.R. §1.20(j)(1), please charge the sum of \$1,120.00 to Deposit Account No. 16-1445 for the filing of this application of extension of patent term. Also, please charge any underpayment, or any additional fees that may be

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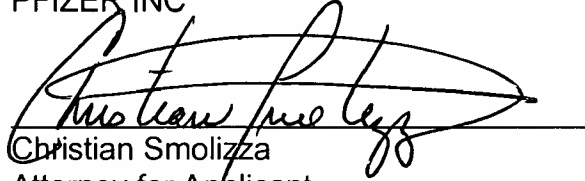
Attorney Docket No. PC10925A
Express Mail No. EF321670551US

- 2 -

required, or credit any overpayment, to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

Respectfully submitted,
PFIZER INC

Date: October 3, 2007



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PFIZER INC.
Legal Division
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New York, NY 10017-5755



Attorney Docket No. PC10925A
Express Mail No. EF321670551US

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By

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Christian Smolizza

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE: U.S. PATENT NO. 6,667,314 :
ISSUED: DECEMBER 23, 2003 :
TO: MANOUSSOS PERROS, DAVID ANTHONY :
PRICE, BLANDA LUZIA CHRISTA STAMMEN and :
ANTHONY WOOD :
FOR: TROPANE DERIVATIVES USEFUL IN THERAPY :
FROM: SERIAL NO. 09/865,950 :
OF: MAY 25, 2001 :

Commissioner for Patents
Mail Stop Patent Extension
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

APPLICATION FOR EXTENSION OF THE TERM OF
UNITED STATES PATENT NO. 6,667,314 UNDER 35 U.S.C. §156
FOR SELZENTRYTM (MARAVIROC) TABLETS

Your applicant, PFIZER INC., a corporation organized and existing under the laws of the State of Delaware, and having a place of business at 235 East 42nd Street, New York, NY 10017, United States of America, represents that it is the owner of the entire right, title and interest in and to Letters Patent of the United States No. 6,667,314 granted to MANOUSSOS PERROS, DAVID ANTHONY PRICE, BLANDA LUZIA CHRISTA STAMMEN and ANTHONY WOOD on the 23rd day of December 2003 for TROPANE DERIVATIVES USEFUL IN THERAPY, by virtue of assignments, recorded in the United States Patent and Trademark Office (hereinafter referred to as "the Patent

Office") on the 6th day of May, 2002 at Reel 012880, Frame 0636. A copy of the Notice of Recordation is enclosed as Exhibit A.

Pursuant to the provisions of 37 C.F.R. §1.730, your applicant hereby applies for an extension of the term of Patent No. 6,667,314 under 35 U.S.C. §156 of 73 days, based on the materials set forth herein and in the accompanying papers.

In the materials which follow herein, numbered paragraphs (1) through (15) correspond to paragraphs (1) through (15) of 37 C.F.R. §1.740(a).

(1) The approved product is SELZENTRY™ (maraviroc) Tablets. SELZENTRY™ Tablets consist of maraviroc and pharmaceutically-acceptable carriers. Maraviroc is further identified as follows:

Chemical Name

4,4-difluoro-N-{(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclohexanecarboxamide

Alternate Chemical Name

N-{(1S)-3-[3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-4,4-difluorocyclohexanecarboxamide; and

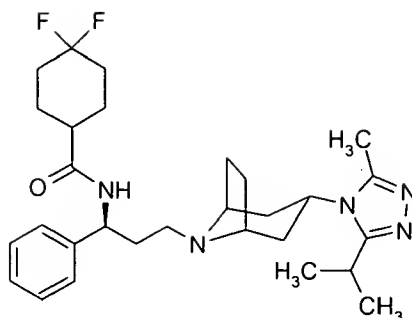
Molecular Formula

C₂₉H₄₁F₂N₅O

Molecular Weight

513.67

Chemical Formula



Physical Description

SELZENTRY™ film-coated tablets contain 150 or 300 mg of maraviroc and the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate (anhydrous), sodium starch glycolate, and magnesium stearate. The film-coat [Opadry® II Blue (85G20583)] contains FD&C blue #2 aluminum lake, soya lecithin, polyethylene glycol (macrogol 3350), polyvinyl alcohol, talc and titanium dioxide.

(2) SELZENTRY™ (maraviroc) tablets was subject to regulatory review under section 505(b) of the Federal Food, Drug and Cosmetic Act, which is codified at 21 U.S.C. §355(b).

(3) SELZENTRY™ (maraviroc) tablets received permission for commercial marketing or use under section 505(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §355(b), on August 6, 2007. It was approved for combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1 detectable, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

(4) The active ingredient in SELZENTRY™ tablets is maraviroc. Maraviroc has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act.

(5) This application is being submitted within the sixty day period permitted for its submission pursuant to 37 C.F.R. §1.720(f). The last day on which this application could be submitted is October 4, 2007.

(6) The patent for which an extension is being sought is identified as follows:

Inventors: MANOUSSOS PERROS, DAVID ANTHONY PRICE,
BLANDA LUZIA CHRISTA STAMMEN and ANTHONY WOOD

Patent No.: 6,667,314

For: TROPANE DERIVATIVES USEFUL IN THERAPY

Issued: DECEMBER 23, 2003

Expires: MAY 25, 2021

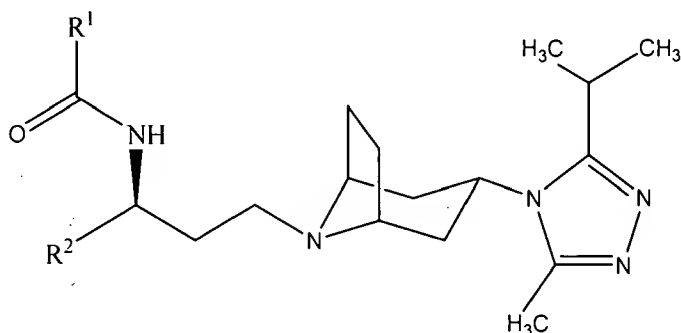
(7) A copy of Patent No. 6,667,314, the patent for which an extension is being sought, is attached hereto as Exhibit B.

(8) A maintenance fee payment for Patent No. 6,667,314 has been made to keep the patent in force beyond four years from its issue date. A copy of the official receipt for such payment is attached hereto as Exhibit C. Patent No. 6,667,314 has no disclaimers, certificates of correction or re-examination certificates.

(9) Patent No. 6,667,314 claims the approved product, pharmaceutical compositions including the approved product, and a method of using the approved product. Claims 1, 3, 4, 5, 6, 7, 8 and 34 claim the approved product; claim 9 claims a pharmaceutical composition which contains the approved product and is useful for the approved use; claim 10 claims the approved use of the approved product; and claim 30 claims a method of manufacturing the approved product. A showing that lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product, a pharmaceutical composition containing the approved product, or a method of using the approved product is as follows:

Claim 1 of Patent No. 6,667,314 reads as follows:

"A compound of the formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

R¹ is C₃₋₆ cycloalkyl optionally substituted by one or more fluorine atoms, or C₁₋₆ alkyl optionally substituted by one or more fluorine atoms, or C₃₋₆ cycloalkylmethyl optionally ring-substituted by one or more fluorine atoms; and

R² is phenyl optionally substituted by one or more fluorine atoms.

In claim 1 when R₁ is a C₆ cycloalkyl (cyclohexyl) group substituted with two fluorine atoms and R² is phenyl, the compound claimed is maraviroc. Therefore, claim 1 reads on the approved product.

Claim 3 depends on claim 1, wherein R¹ is either C₄₋₆ cycloalkyl optionally substituted by one or two fluorine atoms, or C₁₋₄ alkyl optionally substituted by from one to three fluorine atoms. When R¹ is a C₆ cycloalkyl (cyclohexyl) group substituted by two fluorine atoms and R² is phenyl, the compound is maraviroc. Therefore, claim 3 reads on the approved product.

Claim 4 depends on claim 3, wherein R¹ is either cyclobutyl, cyclopentyl, 4,4-difluorocyclohexyl or 3,3,3-trifluoropropyl. When R¹ is 4,4-difluorocyclohexyl and R² is phenyl, the compound is maraviroc. Therefore, claim 4 reads on the approved product.

Claim 5 depends on claim 1, wherein R² is phenyl optionally substituted by 1 or 2 fluorine atoms. When R₁ is a C₆ cycloalkyl (cyclohexyl) group substituted with two

fluorine atoms and R² is phenyl, the compound is maraviroc. Therefore, claim 5 reads on the approved product.

Claim 6 depends on claim 5, wherein R² is phenyl or monofluorophenyl. When R¹ is a C₆ cycloalkyl (cyclohexyl) group substituted with two fluorine atoms and R² is phenyl, the compound is maraviroc. Therefore, claim 6 reads on the approved product.

Claim 7 depends on claim 6, wherein R² is phenyl or 3-fluorophenyl. When R¹ is a C₆ cycloalkyl (cyclohexyl) group substituted with two fluorine atoms and R² is phenyl, the compound is maraviroc. Therefore, claim 7 reads on the approved product.

Claim 8 depends on claim 1, which is selected from the group consisting of
N-((1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)cyclobutanecarboxamide;
N-((1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)cyclopentanecarboxamide;
N-((1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4,4-trifluorobutanamide;
N-((1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide; and
N-((1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl)-4,4-difluorocyclohexanecarboxamide; or a pharmaceutically acceptable salt or solvate of any thereof. When the compound is N-((1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide, the compound is maraviroc. Therefore, claim 8 reads on the approved product.

Claim 9 claims a pharmaceutical composition comprising an amount of a compound according to claim 1 and one of a pharmaceutically acceptable excipient, a pharmaceutically acceptable diluent or a pharmaceutically acceptable carrier. Since

claim 1 claims a compound which encompasses maraviroc as previously described, claim 8 reads on a pharmaceutical composition comprising the approved product.

Claim 10 claims a method antagonizing a CCR5 receptor in a mammal, comprising administering to said mammal in need thereof an effective amount of a compound of claim 1 to antagonize the CCR5 receptor-associated responses in said mammal. Maraviroc is approved for combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1 detectable, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. Claim 1 claims a compound which encompasses maraviroc as previously described, claim 10 reads on a method of using the approved product for the approved use.

Claim 30 claims a process for the preparation of a compound of claim 1. When R^1 is a C_6 cycloalkyl (cyclohexyl) group substituted with two fluorine atoms, R^2 is phenyl, and when a compound of formula (XVI) and a compound of formula (VIA) undergoes reductive amination (step (d)), the compound prepared is maraviroc. Therefore, claim 30 reads on the approved product.

Claim 34 claims a compound of claim 1 which is N-((1S)-3-[3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide or a pharmaceutically acceptable salt. When the compound is N-((1S)-3-[3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide, the compound is maraviroc. Therefore, claim 34 reads on the approved product.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

- An exemption under subsection (i) of section 505 of the Federal Food, Drug and Cosmetic Act became effective for SELZENTRY™ (maraviroc) Tablets June 10, 2003, (attached hereto as Exhibit D), following receipt by the Food and Drug Administration of Investigational New Drug ("IND") Application No. 65,229 on May 7, 2003.
- A New Drug Application ("NDA") under section 505(b) of the Federal Food, Drug and Cosmetic Act for SELZENTRY™ (maraviroc) Tablets was initially submitted on December 19, 2006, as NDA No. 22-128.
- NDA No. 22-128 was approved on August 6, 2007.

(11) A brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities is attached hereto as Exhibit E.

(12) Applicant is of the opinion that Patent No. 6,667,314 is eligible for an extension under 35 U.S.C. §156. The length of extension claimed is 73 days.

The eligibility requirements of 35 U.S.C. §§156(a) and 156(c)(4) have been satisfied as follows:

- Patent No. 6,667,314 claims a product, SELZENTRY™ (maraviroc) Tablets, pharmaceutical compositions including the product, SELZENTRY™ (maraviroc) Tablets, and a method of using the product, SELZENTRY™ (maraviroc) Tablets
- Patent No. 6,667,314 is currently set to expire on May 25, 2021 (*i.e.*, the term of the patent has not yet expired).
- The term of Patent No. 6,667,314 has never been extended under subsection (e)(1) of 35 U.S.C. §156.
- This application for extension is being submitted by PFIZER INC, the owner of record of Patent No. 6,667,314, in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. §156(d).
- The product, SELZENTRY™ (maraviroc) Tablets, has been subject to a regulatory review period under section 505(b) of the Federal Food, Drug and Cosmetic Act before its commercial marketing or use, and the permission for said commercial marketing or use is the first permitted commercial marketing or use of the product under section 505(b) of the Federal Food, Drug and Cosmetic Act.
- No patent has to this date been extended, nor has any other extension been applied for, under subsection (e)(1) of 35 U.S.C. §156, for the regulatory review period which forms the basis for this application for extension of the term of Patent No. 6,667,314.

The length of extension of the term of Patent No. 6,667,314 of 73 days claimed by applicant was determined according to the provisions of 37 C.F.R. §1.775 as follows:

- According to 37 C.F.R. §1.775(b), the length of extension is equal to the regulatory review period for the approved product, reduced as appropriate pursuant to paragraphs (d)(1) through (d)(6) of 37 C.F.R. §1.775.
- According to 37 C.F.R. §1.775(c), the regulatory review period is the sum of: (A) the number of days in the period beginning on the date the exemption under subsection 505 of the Federal Food, Drug and Cosmetic Act became effective for the approved product and ending on the date the NDA was initially submitted under subsection 505 of the Federal Food, Drug and Cosmetic Act; and (B) the number of days in the period beginning on the date the NDA was initially submitted under subsection 505 of the Federal Food, Drug and Cosmetic Act and ending on the date the NDA was approved. The exemption under subsection 505(i) of the Federal Food, Drug and Cosmetic Act became effective on June 10, 2003; the NDA was initially submitted on December 19, 2006; and the NDA was approved on August 6, 2007. Hence, the regulatory review period under 37 C.F.R. §1.775(c) is the sum of the period from June 10, 2003, the IND effective date, to December 19, 2006, the NDA submission date, and from December 19, 2006, the NDA submission date, to August 6, 2007, the NDA approval date. This is the sum of 1,288 days and 230 days, which is 1,518 days.
- According to 37 C.F.R. §1.775(d)(1)(i), the number of days in the regulatory review period which were on and before the date on which the patent issued must be subtracted. Patent No. 6,667,314 issued on December 23, 2003. Subtraction of the period on and before December 23, 2003 leaves a reduced regulatory review period from December 24, 2003 to December 19, 2006 and from December 19, 2006 to August 6, 2007. This is the sum of 1,091 days and 230 days, which is 1,321 days.
- 37 C.F.R. §1.775(d)(1)(ii) does not apply.
- According to 37 C.F.R. §1.775(d)(1)(iii), the regulatory review period must then be reduced by one-half of the days remaining in the period defined in 37 C.F.R.

§1.775(c)(1). This is one-half of 1,091 days, which is 545.5 (rounded up to 546) days. After subtraction, this now leaves a reduced regulatory review period of 546 days plus 230 days, which is 776 days.

- According to 37 C.F.R. §1.775(d)(2), the reduced regulatory review period of 776 days must be added to the expiration date of Patent No. 6,667,314 (*i.e.*, May 25, 2021). This gives a date of July 10, 2023. According to 37 C.F.R. §1.775(d)(3), 14 years must be added to the date of approval of the approved product. This gives a date of August 6, 2021. According to 37 C.F.R. §1.775(d)(4), the earlier of these dates must be selected. The earlier of these dates is August 6, 2021 (*i.e.*, 73 days beyond the expiration date of the 6,667,314 patent).
- The provisions of 37 C.F.R. §1.775(d)(5) apply to this application, because Patent No. 6,667,314 issued after September 24, 1984. Pursuant to 37 C.F.R. §1.775(d)(5)(i) five (5) years are added to the expiration date of Patent No. 6,667,314 (May 25, 2021) giving a date of May 25, 2026. According to 37 C.F.R. §1.775(d)(5)(ii), the dates obtained pursuant to 37 C.F.R. §1.775(d)(5)(i) and 37 C.F.R. §1.775(d)(4) are compared and the earlier date is selected. The date calculated according to 37 C.F.R. §1.775(d)(4) above is August 6, 2021. Therefore, the earlier of these dates is August 6, 2021. Applicant is entitled to an extension of term of Patent No. 6,667,314 until August 6, 2021, *i.e.*, an extension of 73 days from the original expiration date of May 25, 2021.
- 37 C.F.R. §1.775(d)(6) does not apply because Patent No. 6,667,314 issued on June 25, 2002, after September 24, 1984.

(13) Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension of 73 days which is being sought to the term of Patent No. 6,667,314.

Attorney Docket No. PC10925A
Express Mail No. EF321670551US

(14) The prescribed fee under 37 C.F.R. §1.20(j)(1) for receiving and acting on this application for patent term extension is to be charged to Deposit Account No. 16-1445, as requested in the enclosed transmittal letter.

(15) Please direct all inquiries and correspondence relating to this application for patent term extension as follows:

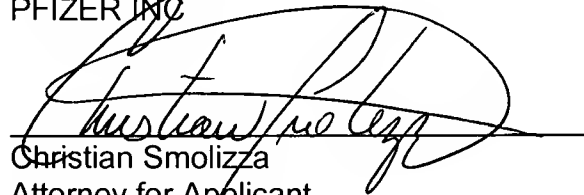
Christian Smolizza, Esq.
Corporate Counsel
PFIZER INC.
Legal Division
Patent Department (150/05/43S)
150 East 42nd Street
New York, NY 10017-5755

Tel: (212) 733-9094
Fax: (212) 573-1939

Pursuant to 37 C.F.R. §1.740(b), two duplicate copies of these application papers are enclosed herewith. Pursuant to M.P.E.P. §2753 an additional two copies of the application are also enclosed herewith. Accordingly, a total of four copies of the application and one original application for patent term extension of Patent No. 6,667,314 are submitted herewith.

Applicant respectfully requests prompt and favorable action on the merits of this application for extension of the term of Letters Patent No. 6,667,314 of 73 days, based on the regulatory review period for SELZENTRY™ (maraviroc) Tablets.

Respectfully submitted,
PFIZER INC

A handwritten signature in black ink, appearing to read "Christian Smolizza", is written over a horizontal line.

Christian Smolizza
Attorney for Applicant
Reg. No. 46,319
Tel.: (212) 733-9094
Fax: (212) 573-1939

Date: October 3, 2007

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Legal Division
150 East 42nd Street
New York, NY 10017-5755

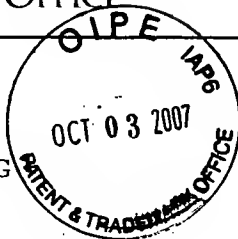


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JULY 15, 2002

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PTAS

PFIZER INC
PATENT DEPT. - NYC

Chief Information Officer
Washington, DC 20231
www.uspto.gov



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UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 05/06/2002

REEL/FRAME: 012880/0636
NUMBER OF PAGES: 2

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

PERROS, MANOUSSOS

DOC DATE: 03/05/2001

ASSIGNOR:

PRICE, DAVID ANTHONY

DOC DATE: 03/05/2001

ASSIGNOR:

STAMMEN, BLANDA LUIZA CHRISTA

DOC DATE: 03/05/2001

ASSIGNOR:

WOOD, ANTHONY

DOC DATE: 03/05/2001

ASSIGNEE:

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235 EAST 42ND STREET, 20TH FLOOR
NEW YORK, NEW YORK 10017-5755

ASSIGNEE:

PFIZER PRODUCTS INC.
EASTERN POINT ROAD
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GROTON, CONNECTICUT 06340

EXPRESS MAIL NO. EF32167055145

012880/0636 PAGE 2

SERIAL NUMBER: 09865950
PATENT NUMBER:

FILING DATE: 05/25/2001
ISSUE DATE:

JOANN STEWART, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

05-15-2002

1-31-92

Patent and Trademark

To the Director - United States Patent and Trademark Office

or copy thereof.

1. Name of conveying party(ies):

Manoussos PERROS, David Anthony PRICE, Blanda
Luiza Christa STAMMEN and Anthony WOODAdditional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

3. Nature of conveyance:

- ☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other

Execution Date: March 05, 2001

2. Name and address of receiving party(ies):

Name: Pfizer Inc.Street Address: 235 East 42nd Street, 20th FloorCity: New York State: New York Zip: 10017-5755

and

Name: Pfizer Products Inc.Internal Address: Bldg. 188S, 3rd FloorStreet Address: Eastern Point RoadCity: Groton State: Connecticut Zip: 06340Additional name(s) & address(es) attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)

B. Patent No. (s)

09/865,950Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Paul H. GinsburgInternal Address: Pfizer IncStreet Address: 235 East 42nd Street, 20th FloorCity: New York State: New York ZIP: 10017-5755

6. Total number of pages including cover sheet, attachments and document: 3

7. Total fee (37 CFR 3.41).....\$ 40.00☐ Enclosed☒ Authorized to be charged to deposit account

8. Deposit account number:

16-1445

(Attach duplicate copy of this page if paying by deposit account)

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9. Statement and signature.

*To the best of my knowledge and belief, the foregoing information is true and correct and any attached document is the original or a true copy of the original document.*J. N. Myers

Name of Person Signing

Signature

Date

Total number of pages including cover sheet: 3

OMB No. 0651-0011 (exp. 4/94)

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Director - United States Patent and Trademark Office

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Joint Inventors
Pfizer - US Only**ASSIGNMENT**

For valuable consideration, the receipt and adequacy of which is hereby acknowledged we **Manoussos Perros, David Anthony Price, Blanda Luzia Christa Stammen and Anthony Wood** of Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom respectively, hereby sell, assign and transfer unto **PFIZER INC.**, a corporation organised and existing under the laws of the State of Delaware, and having a place of business at 235 East 42nd Street, New York, N.Y. 10017, United States of America, the entire right, title, and interest in and to our application for Letters Patent of the United States, executed the 05 day of March 2001 entitled **TROPANE DERIVATIVES USEFUL IN THERAPY** and our entire right, title and interest in the United States in and to all our inventions, whether joint or sole, disclosed in said application for Letters Patent, and in and to all United States patents granted on the foregoing inventions, and we hereby agree, whenever requested, to communicate to said assignee, its successors and assigns, any facts known to us respecting said inventions, to testify in any legal proceeding, and to execute all applications or papers necessary to obtain and maintain proper patent protection on said inventions in the United States.

Signed and witnessed this 05 day of March 2001
at Sandwich, Kent, England.

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(12) **United States Patent**
Perros et al.

(10) Patent No.: **US 6,667,314 B2**
(45) Date of Patent: **Dec. 23, 2003**

(54) **TROPANE DERIVATIVES USEFUL IN THERAPY**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(60) Provisional application No. 60/214,587, filed on Jun. 27, 2000, and provisional application No. 60/219,202, filed on Jul. 19, 2000.

(30) **Foreign Application Priority Data**

Jun. 27, 2000 (GB) 0015835

(51) Int. Cl.⁷ **A61K 31/46; C07D 451/04; A61P 29/00; A61P 31/18**

(52) U.S. Cl. **514/304; 546/125; 560/37; 560/38; 564/191**

(58) Field of Search **546/125; 514/304; 560/38; 564/191**

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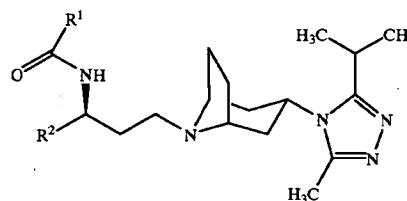
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(57) **ABSTRACT**

The present invention provides compounds of the formula:



wherein R¹ is C₃₋₆ cycloalkyl optionally substituted by one or more fluorine atoms, or C₁₋₆ alkyl optionally substituted by one or more fluorine atoms, or C₃₋₆ cycloalkylmethyl optionally ring-substituted by one or more fluorine atoms; and

R² is phenyl optionally substituted by one or more fluorine atoms, to pharmaceutically acceptable salts and solvates thereof, and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such compounds.

35 Claims, No Drawings

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TROPANE DERIVATIVES USEFUL IN THERAPY

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority of foreign application numbers GB 0014046.7 and GB 0015835.2, filed in Great Britain on May 26, 2000 and Jun. 27, 2000, respectively. This application also claims the benefit of priority of U.S. Provisional Application Nos. 60/214,587 and 60/219,202, filed Jun. 27, 2000 and Jul. 19, 2000, respectively.

This invention relates to tropane derivatives useful in the treatment of a variety of disorders, including those in which the modulation of CCR5 receptors is implicated. More particularly, the present invention relates to 3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]octane derivatives and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives. Disorders that may be treated or prevented by the present derivatives include HIV and genetically related retroviral infections (and the resulting acquired immune deficiency syndrome, AIDS), and inflammatory diseases.

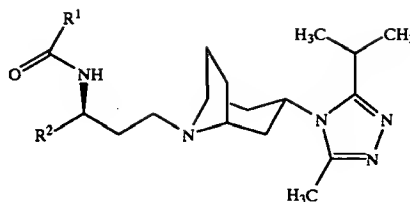
The compounds of the present invention are modulators, especially antagonists, of the activity of chemokine CCR5 receptors. Modulators of the CCR5 receptor may be useful in the treatment of various inflammatory diseases and conditions, and in the treatment of infection by HIV-1 and genetically related retroviruses. The name "chemokine", is a contraction of "chemotactic cytokines". The chemokines comprise a large family of proteins which have in common important structural features and which have the ability to attract leukocytes. As leukocyte chemotactic factors, chemokines play an indispensable role in the attraction of leukocytes to various tissues of the body, a process which is essential for both inflammation and the body's response to infection. Because chemokines and their receptors are central to the pathophysiology of inflammatory and infectious diseases, agents which are active in modulating, preferably antagonizing, the activity of chemokines and their receptors, are useful in the therapeutic treatment of such inflammatory and infectious diseases.

The chemokine receptor CCR5 is of particular importance in the context of treating inflammatory and infectious diseases. CCR5 is a receptor for chemokines, especially for the macrophage inflammatory proteins (MIP) designated MIP-1 α and MIP-1 β , and for a protein which is regulated upon activation and is normal T-cell expressed and secreted (RANTES).

There has been a substantial investigation of different classes of modulators of chemokine receptor activity, especially that of the CCR5 chemokine receptor, for example, WO 98/25617 relates to substituted aryl piperazines as modulators of chemokine receptor activity.

The present compounds are generally disclosed by WO 00/38680 but none is specifically exemplified therein.

According to a first aspect of the present invention, there is provided a compound of formula (I),

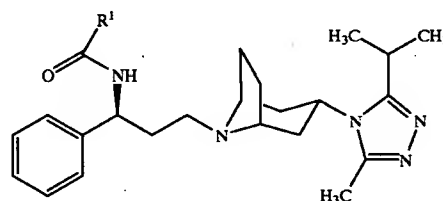


wherein R¹ is C₃₋₆ cycloalkyl optionally substituted by one or more fluorine atoms, or C₁₋₆ alkyl optionally substituted by one or more fluorine atoms, or C₃₋₆ cycloalkyl-methyl optionally ring-substituted by one or more fluorine atoms; and

R² is phenyl optionally substituted by one or more fluorine atoms;

or a pharmaceutically acceptable salt or solvate thereof.

According to a second aspect of the present invention, there is provided a compound of formula (IA),



wherein R¹ represents either C₃₋₆ cycloalkyl optionally substituted by one or more fluorine atoms, or C₁₋₆ alkyl optionally substituted by one or more fluorine atoms, or a pharmaceutically acceptable salt or solvate thereof.

"C₁₋₆ alkyl" in the definition of R¹ includes straight-chain and branched groups. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. "C₃₋₆ cycloalkyl" means cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The compounds of formula (I) contain a basic centre and suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, camsylate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate and pamoate salts. For a review on suitable salts see Berge et al, J. Pharm. Sci., 66, 1-19, 1977.

The pharmaceutically acceptable solvates of the compounds of the formula (I) or salts thereof include the hydrates thereof.

Also included within the present scope of the compounds of the formula (I) are polymorphs thereof.

A compound of the formula (I) contains one or more asymmetric carbon atoms and therefore exists in two or more stereoisomeric forms. The present invention includes the individual stereoisomers of the compounds of the formula (I) and, where appropriate, the individual tautomeric forms thereof, together with mixtures thereof.

Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable

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chiral support or by fractional crystallisation of the diastereoisomeric salts formed by; reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

The invention also includes isotopically labelled compounds of the formula (I).

Preferably, R^1 is either C_{4-6} cycloalkyl optionally substituted by one or two fluorine atoms, or C_{1-4} alkyl optionally substituted by from one to three fluorine atoms.

Preferably, R^1 is either cyclobutyl, cyclopentyl, 4,4-difluorocyclohexyl or 3,3,3-trifluoropropyl.

Preferably, R^2 is pbenyl optionally substituted by 1 or 2 fluorine atom(s).

Preferably, R^2 is pbenyl or monofluoropbenyl.

Preferably, R^2 is phenyl or 3-fluorophenyl.

Preferred compounds of the formula (I) include N-((1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)cyclobutanecarboxamide;

N-((1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)cyclopentanecarboxamide;

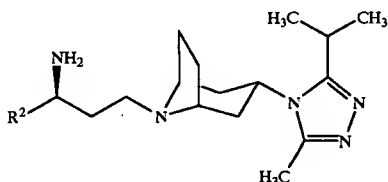
N-((1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-pbenylpropyl)-4,4,4-trifluorobutanamide;

N-((1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-pbenylpropyl)-4,4-difluorocyclohexanecarboxamide; and

N-((1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluoropbenyl)propyl)-4,4-difluorocyclohexanecarboxamide; or a pharmaceutically acceptable salt or solvate of any thereof.

The compounds of the formula (I) may be prepared by the following general methods in which R^1 and R^2 are as previously defined for a compound of the formula (I) unless otherwise stated.

1. A compound of the formula (I) may be prepared by reacting a compound of formula:



with a compound of formula:



under conventional coupling conditions.

The reaction is preferably carried out in the presence of a suitable coupling agent (for example, N-benzyl-N'-cyclohexylcarbodiimide (which may be polymer-bound), or hydroxybenzotriazole hydrate and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide), at about room temperature, in a solvent that does not adversely affect the reaction, for example, dichloromethane. Further suitable coupling conditions are described in Method 2 below.

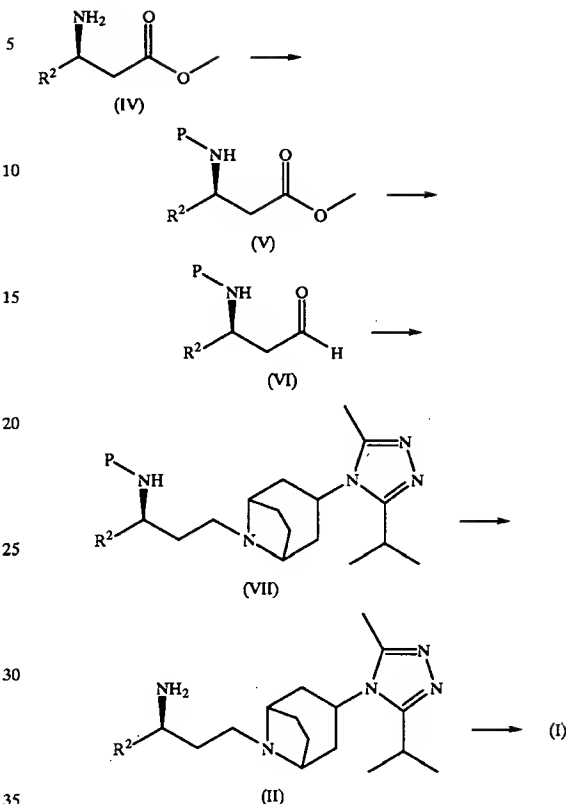
The compounds of formula (III) are either known or are prepared using conventional techniques.

The compounds of the formula (II) may be prepared as shown in Scheme 1 below.

2. The compounds of the formula (I) may be prepared as shown in Scheme 1.

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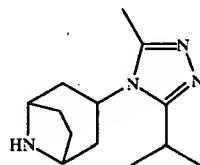
Scheme 1



wherein P is a suitable protecting group such as t-butyloxycarbonyl, benzyl or benzyloxycarbonyl and the compounds of the formula (II) and (VII) are in the exo form. In a typical procedure, where P is t-butyloxycarbonyl, an amine of the formula (IV) is reacted with di-tert-butyl dicarbonate in the presence of a base acceptor such as aqueous sodium hydroxide and in a suitable solvent such as tetrahydrofuran.

The protected amine of the formula (V) may be reduced to an aldehyde of the formula (VI) using a suitable reducing agent, e.g., using diisobutylaluminium hydride in dichloromethane at below -70° C.

Reductive amination reaction of the aldehyde of the formula (VI) with an amine of the formula (I) (in the exo form):



leads to a compound of the formula (VII). The reaction may be carried out in the presence of an excess of a suitable reducing agent, e.g. sodium triacetoxyborohydride or sodium cyanoborohydride, in a protic solvent system e.g., acetic acid in either dichloromethane or 1,1,1-trichloroethane, at room temperature.

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Deprotection of a compound of the formula (VII) may be accomplished using conventional conditions. Where P is t-butyloxycarbonyl this may be achieved using trifluoroacetic acid or aqueous hydrochloric acid in a solvent such as dichloromethane or methanol at room temperature.

A compound of the formula (II) prepared may be converted to a compound of the formula (I) by reaction with a compound of the formula:



(VIB)

wherein Z is a carboxylic acid activating group such as chloro or 1H-imidazol-1-yl, using conventional conditions, e.g. using N,N'-carbonyldiimidazole, triethylamine and dichloromethane.

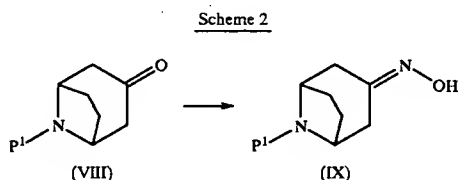
Preferably, a compound of the formula (VIB) is generated in situ from a compound of the formula (III) using a carbodiimide such as 3-(3-dimethylamino-1-propyl)-1-ethylcarbodiimide or N-benzyl-N'-cyclohexylcarbodiimide-polymer bound, optionally in the presence of 1-hydroxybenzotriazole hydrate, and reacted with a compound of the formula (II). The reaction may be performed in a suitable solvent such as dichloromethane, tetrahydrofuran or ethyl acetate, optionally in the presence of a base such as a tertiary amine, e.g. triethylamine or N-ethyl-diisopropylamine, at about room temperature.

Alternatively, the acid of the formula (III) may be first activated with benzotriazol-1-yloxy-tris(dimethylamino) phosphonium hexafluorophosphate (BOP), bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PYBROP), or 2-fluoro-1-methylpyridinium p-toluenesulphonate (Mukaiyama's reagent) in the presence of an excess of N-methylmorpholine, triethylamine or N-ethyl-diisopropylamine in a suitable solvent such as tetrahydrofuran, dichloromethane or ethyl acetate, at room temperature to provide a compound of the formula (VIB) and this is reacted with a compound of the formula (II).

Alternatively, an acid chloride of formula (VIB) wherein Z is chloro may be reacted with a compound of the formula (II), optionally in the presence of a suitable base, e.g. triethylamine, N-ethyl-diisopropylamine, sodium carbonate, potassium carbonate or sodium bicarbonate, and in a suitable solvent such as dichloromethane, ethyl acetate, THF or toluene, at room temperature.

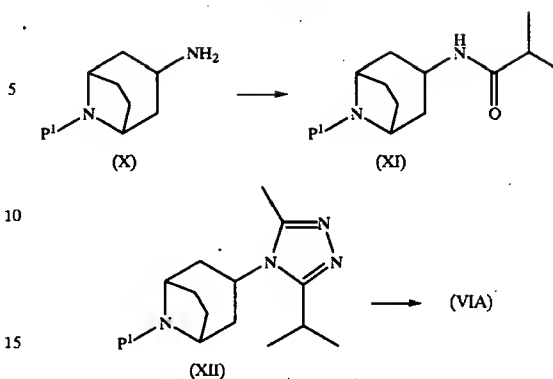
It will be appreciated that the transformation of a compound of the formula (VII) to a compound of the formula (I) via a compound of the formula (II) can be performed in a "one-pot procedure" by deprotection/coupling using similar methods to those previously described.

A compound of the formula (VIA) may be prepared as shown in Scheme 2.



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-continued



wherein P¹ is a suitable protecting group such as t-butyloxycarbonyl or benzyl and the compounds of the formulae (X), (XI) and (XII) are in the exo form.

An oxime of the formula (IX) may be prepared by the condensation of a ketone of the formula (VIII) with hydroxylamine hydrochloride in the presence of a base, e.g. pyridine, and in a suitable solvent, typically ethanol. The reaction is typically carried out at the reflux temperature of the solvent.

Where P¹ is t-butyloxycarbonyl or benzyl, reduction of an oxime of the formula (IX) may be achieved using sodium in the presence of an alcohol, typically pentanol, or by electrochemical reduction, to provide an amine of the formula (X).

An amide of the formula (XI) may be prepared by coupling the protected amine of the formula (X) with 2-methylpropanoic acid, or an activated derivative thereof.

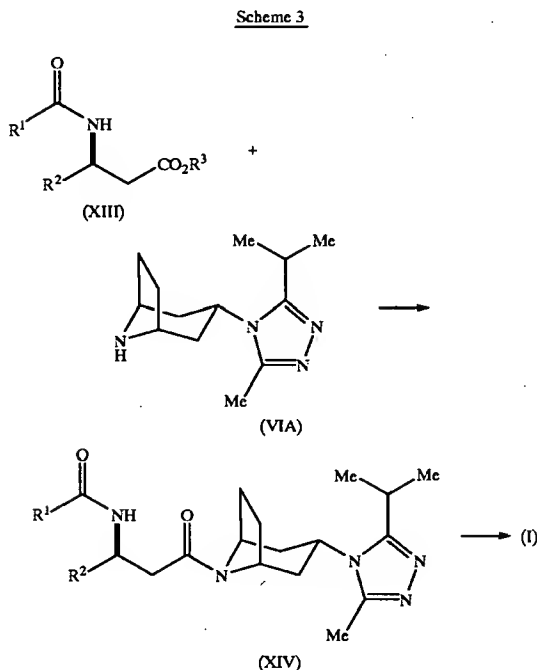
The coupling may be achieved using conventional amide bond forming techniques, such as as described in Methods 1 and 2 above. Typically, the acid may be first activated using a carbodiimide such as 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide, optionally in the presence of 1-hydroxybenzotriazole, in a suitable solvent such as dichloromethane, and in the presence of a base, e.g. a tertiary amine such as triethylamine or diisopropylamine, and then reacted with the amine of the formula (X). Alternatively, the reaction may be performed using 2-methylpropanoyl chloride in the presence of a base such as sodium carbonate and a suitable solvent, e.g. dichloromethane.

A triazole of the formula (XII) may be prepared in a "one-pot", two-step procedure by first coupling an amide of the formula (XI) with acetic hydrazide followed by in-situ cyclo-condensation. Typically, the amide is first activated with phosphorous oxychloride in a solvent such as chloroform and in the presence of a base, e.g. pyridine, at 0° C., then treated with acetic hydrazide in a suitable solvent, e.g. chloroform, and the reaction heated under reflux. The reaction may be driven to completion in the presence of an acid, e.g. p-toluenesulphonic acid, and in a suitable solvent such as toluene at elevated temperature (e.g., 110° C.).

Deprotection of the compound of the formula (XII) using standard methodology provides the amine of the formula (VIA). Typically, where P¹ is benzyl, deprotection is performed by catalytic hydrogenation such as using palladium (II) hydroxide as the catalyst in a suitable solvent, e.g. ethanol, in the presence of ammonium formate at 70+° C. Alternatively, the deprotection may be performed by catalytic hydrogenation using palladium-on-charcoal as the catalyst in a suitable solvent such as methanol, optionally in the presence of a suitable acid such as p-toluenesulphonic acid.

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3. The compounds of the formula (I) may be prepared as shown in Scheme 3.



wherein R^3 is H or C_1-C_6 alkyl.

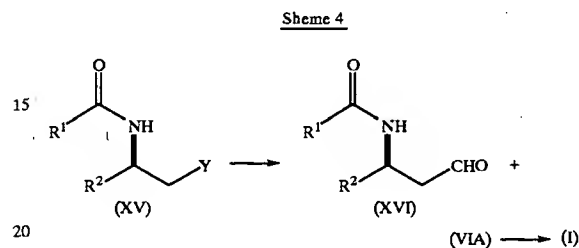
An amide of the formula (XIV) may be formed by conventional amide bond formation techniques such as by first activating an acid of the formula (XIII) (wherein R_2 is H) either as an acid chloride or using other procedures as described above in Methods 1 and 2, followed by reaction with the amine of the formula (VIA). Alternatively an ester of the formula (XIII) (wherein R^3 is C_1-C_6 alkyl) may be reacted directly with the amine or a metal salt thereof. Thus the acid chloride and the amine, or a salt thereof, may be reacted in the presence of an excess of a suitable base, e.g. Na_2CO_3 , $NaHCO_3$, K_2CO_3 , triethylamine or N,N -diisopropylethylamine, and in a suitable solvent, e.g. dichloromethane, ethyl acetate, THF or toluene, with or without water as a co-solvent. Alternatively the acid may be activated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (WCDI), CDI (1,1'-carbonyldiimidazole) or DCC (1,3-dicyclohexylcarbodiimide) and HOAT (1-hydroxy-7-azabenzotriazole) or HOBT (1-hydroxybenzotriazole hydrate), and reacted with the amine in the presence of a base, e.g. triethylamine, in a solvent such as THF, dichloromethane or toluene. Also, the ester and the amine or a metal salt thereof, may be reacted together in the presence of a base, e.g. triethylamine, and an optional catalyst in a solvent such as dichloromethane, ethyl acetate, THF or toluene, with or without water as co-solvent. Alternatively, the ester, the amine and an enzyme-catalyst may be reacted together in a solvent such as dichloromethane, ethyl acetate, THF or toluene, with or without water as co-solvent. Preferably, the acid chloride, the amine and Na_2CO_3 are reacted together in dichloromethane and water, or the acid is treated with N,N' -carbonyldiimidazole to form the imidazolide and then reacted with the amine in dichloromethane in the presence of triethylamine.

The amide of the formula (XIV) may be reduced, such as by using a nucleophilic hydride reagent or an electrophilic

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hydride reagent, or by catalytic hydrogenation, or by using an alkyl or aryl-silane with a suitable transition metal catalyst, to provide a compound of the formula (I). Typical conditions include using Red-Al® (sodium bis(2-methoxyethoxy)aluminum hydride) in THF or toluene, or borane in THF.

4. The compounds of the formula (I) may be prepared as shown in Scheme 4.



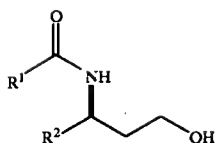
wherein Y is $-CO_2R^4$, $-CN$ or $-C(O)NHR^4$, wherein R^4 is H or C_1-C_6 alkyl

The reaction to prepare an aldehyde of the formula (XVI) may be performed by reduction of an ester, nitrile, or amide of the formula (XV), such as with a hydride reducing agent in a suitable solvent. Alternatively, reduction of an ester, nitrile or acid (activated by a suitable reagent) of the formula (XV) may be achieved with a suitable transition metal catalyst, a hydrogen source and in a suitable solvent. Typical conditions include reducing the ester, nitrile or amide with an aluminum or boron hydride such as DIBAL (diisobutylaluminum hydride), Red-Al®, $LiAl(O(t-Bu))_3$ or $(Me_2CHCH(Me))_2BH$ in a solvent such as THF, dichloromethane or toluene; or reducing the acid chloride with a transition metal catalyst such as Pd/C or Pd/BaSO₄, under hydrogen with a modifier such as 2,4-dimethylpyridine and in solvent such as THF or toluene. Preferred conditions include reducing the ester with DIBAL in dichloromethane or toluene.

A compound of the formula (I) may be prepared by reductive amination using the aldehyde of the formula (XVI) and the amine of the formula (VIA), or salt thereof. Typically the reaction may be performed by reacting the aldehyde with 0.8–1.5 mol eq. of the amine, or salt thereof, optionally in the presence of 0.1–3 mol eq. of a protic acid, with either a reducing agent such as sodium triacetoxyborohydride or sodium cyanoborohydride, or using a catalytic transition metal catalyst such as palladium, platinum or rhodium and a hydrogen source such as molecular hydrogen or ammonium formate, in a suitable solvent such as dichloromethane, acetonitrile, toluene, ethanol or 2-propanol. Preferably the aldehyde is reacted with the tosylate salt of the amine in the presence of sodium triacetoxyborohydride and a trace of acetic acid in dichloromethane at ambient temperature.

An aldehyde of the formula (XVI) may also be prepared from an alcohol of the formula:

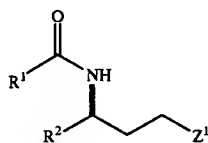
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by standard oxidation techniques, for example, using an oxidising agent such as DMSO/sulphur trioxide-pyridine complex, DMSO with $(\text{COCl})_2$, MoO_3 or CrO_3 , with or without a base, in a suitable solvent such as dichloromethane, toluene, acetone or acetonitrile; using a transition metal catalyst such as Rh or Ru, with or without a base, and a hydride acceptor such as a ketone, in a suitable solvent such as dichloromethane, acetone, toluene or acetonitrile; or using a catalytic oxidant such as TPAP (tetrapropylammonium perruthenate) or TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical), with or without a solid support, with a stoichiometric re-oxidant for the catalyst such as NMO (4-methylmorpholine N-oxide), oxygen or sodium hypochlorite or hypobromite, and in a suitable solvent such as dichloromethane, acetone, toluene or acetonitrile. Preferred conditions include using DMSO, sulphur trioxide-pyridine complex and triethylamine in dichloromethane, or TEMPO, KBr, NaOCl, water and dichloromethane.

5. The compounds of the formula (I) may be prepared by reductive amination of a compound of the formula (XV) wherein Y is $-\text{CN}$ and an amine of the formula (VIA), or salt thereof. The reduction may be performed using a transition metal catalyst, optionally in the presence of an acid, and a hydrogen source, in a suitable solvent. In a typical procedure palladium- α -chloral or platinum (IV) oxide and a solvent such as methanol, acetic acid or 2-propanol are used.

6. The compounds of the formula (I) may be prepared by alkylation of an amine of the formula (VIA), or a salt (acid addition or metal salt) thereof, using a compound of the formula:



wherein Z^1 is a leaving group such as halo, $\text{C}_1\text{-C}_4$ alkylsulphoxyloxy, benzoylsulphoxyloxy or p-toluenesulphoxyloxy, optionally in the presence of a base and/or a phase transfer catalyst.

The reaction may typically be carried out in the presence of a base such as triethylamine or N,N-diisopropylethylamine; DBU (1,8-diazabicyclo[5.4.0]undec-7-ene); or an inorganic base such as Na_2CO_3 , NaHCO_3 , K_2CO_3 or Cs_2CO_3 ; optionally in the presence of a phase transfer catalyst, and in a solvent such as acetonitrile, DMF (dimethylformamide), DMSO (dimethylsulphoxide), 1,4-dioxane, THF or toluene. Alternatively, a metal salt of the amine (i.e. a deprotonated form) may be reacted with a compound of the formula (XVII) in a suitable solvent such as THF, DMF or 1,4-dioxane. Preferably the reaction is carried out by reacting the amine and a compound of the formula (XVII) with either

(XVIIA)

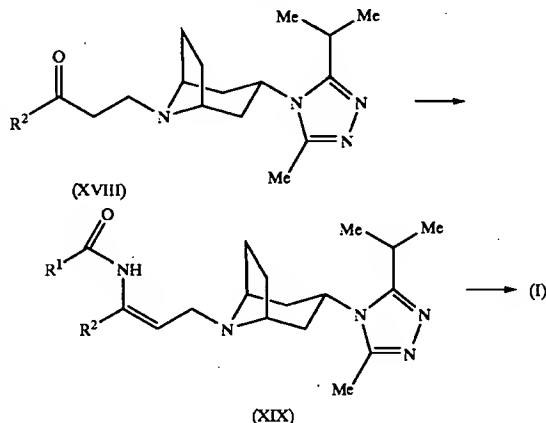
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DBU in acetonitrile or K_2CO_3 and 18-crown-6(1,4,7,10,13,16-hexaoxacyclooctadecane) in THF.

7. The compounds of the formula (I) may be prepared as shown in Scheme 5.

Scheme 5



A compound of the formula (XVIII) may be prepared by the Maillard reaction of a compound of the formula:



with a compound of the formula (VIA), or salt thereof, formaldehyde or an equivalent thereof, with or without acid present, in a suitable solvent. Typical conditions include reacting the amine and the ketone with an acid such as hydrochloric acid, sulphuric acid, p-toluenesulphonic acid or acetic acid, and paraformaldehyde in a suitable solvent such as ethanol, methanol, 2-propanol or DMF; or reacting the amine salt (such as the hydrochloride, sulphate or tosylate salt) with the ketone and paraformaldehyde in a suitable solvent such as ethanol, methanol, 2-propanol or DMF.

Alternatively a compound of the formula (XVIII) may be prepared by reacting a compound of the formula (VIA), or salt thereof, with a compound of the formula:



wherein Z^2 is a leaving group such as as previously defined for Z^1 , using standard alkylation conditions such as as described for Method 6 above.

An enamide of the formula (XIX) may be prepared by reaction of a compound of the formula (XVIII) with an amide of the formula:



under dehydration conditions, with or without an acid catalyst present, and in a suitable solvent; or by reaction of a compound of the formula (XVIII) first with hydroxylamine, or salt thereof, and then reacting the intermediate product with an acid anhydride of the formula:



a transition metal catalyst, and an acid in a suitable solvent; or by reacting a compound of the formula (XVIII) first with ammonia, or a salt thereof, and then reacting the intermediate product with an acid of the formula (III), or an activated derivative thereof, under standard conditions.

(XVII)

45

50

55

60

65

11

Typically a compound of the formula (XVIII) is reacted with an amide of the formula (XXII) in the presence of a catalytic amount of acid with azeotropic removal of water or removal of water using a dehydrating agent such as molecular sieves.

A compound of the formula (I) may be prepared by asymmetric reduction of an enamide of the formula (XIX) such as by using 0.001–0.1 mol eq. of transition metal such as Rh, Ru, Pd, Pt, Ir, or Ti, 0.001–0.2 mol eq. of a chiral ligand such as BINAP (2,2-bis(diphenylphosphino)-1,1'-binaphthyl), tol-BINAP (2,2-bis(di-p-tolylphosphino)-1,1'-binaphthyl), Du-PHOS (1,2-bis(2,5-dimethylphospholano)benzene) or Penn-Phos (P,P'-1,2-phenylenebis(endo-2,5-dimethyl-7-phosphabicyclo[2,2,1]heptane), a hydrogen donor such as molecular hydrogen, phenylsilane, 2-propanol or ammonium formate, and a suitable solvent such as methanol, ethanol, acetonitrile, toluene, ethyl acetate, 2-propanol or THF, at from 0° C. to the reflux temperature and optionally at an elevated pressure.

8. A compound of the formula (I) may be prepared as shown in Scheme 6.

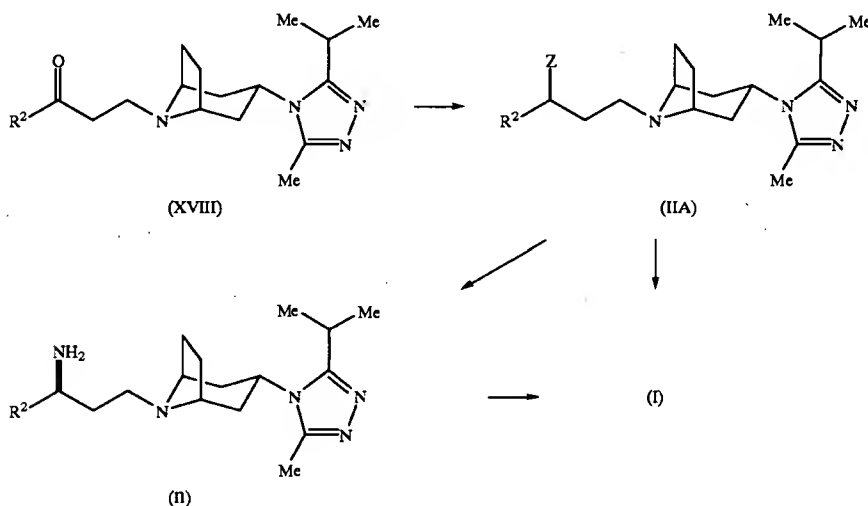
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wherein R⁵ is an ester-forming group such as C₁–C₆ alkyl. Typically the reaction may be carried out by reacting the ester and the amine, or metal salt thereof, with an excess of a base such as triethylamine and an optional catalyst in a solvent such as dichloromethane, ethyl acetate, THF or toluene, with or without water present as a co-solvent; or by reacting the ester and the amine in the presence of an enzyme-catalyst in a solvent such as dichloromethane, ethyl acetate, THF or toluene, with or without water present as a co-solvent.

All of the above reactions and the preparations of novel starting materials using in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the Examples and Preparations hereto.

A pharmaceutically acceptable salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) and the desired

Scheme 6



A ketone of the formula (XVIII) may be converted to a racemic amine of the formula (IIA) by reductive amination under conventional conditions using ammonia, or equivalent thereof, and a reducing agent in a suitable solvent.

The racemic amine of the formula (IIA) may be resolved to provide an amine of the formula (II) by standard techniques such as by using classical, kinetic or dynamic resolution techniques.

The amine of the formula (II) may be converted to a compound of the formula (I) by the routes described in Methods 1 and 2.

Alternatively, a racemic amine of the formula (IIA) may be converted to a compound of the formula (I) using a compound of the formula (III), or a suitable activated derivative thereof, a chiral catalyst, optionally using a catalyst for racemization of the unwanted isomer present, and a suitable solvent.

The amine of the formula (II), or a metal salt thereof (i.e. a deprotonated form), may also be converted to a compound of the formula (I) by reaction with an ester of the formula:



(XXIV)

acid. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

The compounds of formula (I), and their pharmaceutically acceptable salts, are useful because they have pharmacological activity in animals, including humans. More particularly, they are useful in the treatment of a disorder in which the modulation of CCR5 receptors is implicated. Disease states that may be mentioned include HIV, a retroviral infection genetically related to HIV, AIDS, or an inflammatory disease. The compounds of formula (I), and their pharmaceutically acceptable salts, may be administered alone or as part of a combination therapy.

The compounds of this invention may be used for treatment of respiratory disorders, including adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis and chronic sinusitis. Other conditions that may be treated are those triggered, affected or are in any other way correlated with T-cell trafficking in different organs. It is expected that the compounds of this

infectious may be useful for the treatment of such conditions and in particular, but not limited to the following for which a correlation with CCR5 or CCR5 chemokines has been established: inflammatory bowel disease, including Crohn's disease and ulcerative colitis, multiple sclerosis, rheumatoid arthritis, graft rejection, in particular but not limited to kidney and lung allografts, endometriosis, type I diabetes, renal diseases, chronic pancreatitis, inflammatory lung conditions or chronic heart failure. For a recent review of possible applications of chemokines and chemokine receptor blockers see Cascieri, M. A., and Springer, M. S., "The chemokine/chemokine receptor family: potential and progress for therapeutic intervention", *Curr. Opin. Chem. Biol.*, 4(4), 420-7 (Aug. 2000).

The utility of the compounds of formula (I), and their pharmaceutically acceptable salts, as inhibitors of HIV infection may be demonstrated by any one or more methodologies known in the art, such as by using the HIV microculture assays described in Dimitrov et al., *J. Clin. Microbiol.*, 28, 734-737 (1990), and the pseudotyped HIV reporter assay described in Connor et al., *Virology*, 206 (2) 935-44 (1995).

The ability of the compounds of formula (I), and their pharmaceutically acceptable salts, to modulate chemokine receptor activity is demonstrated by methodology known in the art, such as by using the assay for CCR5 binding following procedures disclosed in Combadiere et al., *J. Leukoc. Biol.*, 60, 147-52 (1996); and/or by using the intracellular calcium mobilization assays as described by the same authors. Cell lines expressing the receptor of interest include those naturally expressing the receptor, such as PM-1, or IL-2 stimulated peripheral blood lymphocytes (PBL), or a cell engineered to express a recombinant receptor, such as CHO, 300.19, L1.2 or HEK-293.

The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds of the formula (I) can be administered orally, buccally or sublingually in the form of tablets, capsules, multi-particulates, gels, films, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications. The compounds of the formula (I) may also be administered as fast-dispersing or fast-dissolving dosage forms or in the form of a high energy dispersion or as coated particles. Suitable formulations of the compounds of the formula (I) may be in coated or uncoated form, as desired.

Such solid pharmaceutical compositions, for example, tablets, may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycol and starch (preferably corn, potato or tapioca starch), disintegrants such as sodium starch glycolate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

General Example

A formulation of the tablet could typically contain from 0.01 mg to 500 mg of active compound whilst tablet fill weights may range from 50 mg to 1000 mg. An example of a formulation for a 10 mg tablet is illustrated below:

Ingredient	% w/w
Compound of the formula (I) or salt	10.000*
Lactose	64.125
Starch	21.375
Croscarmellose sodium	3.000
Magnesium stearate	1.500

*Quantity adjusted in accordance with drug activity.

The tablets are manufactured by a standard process, for example, direct compression or a wet or dry granulation process. The tablet cores may be coated with appropriate overcoats.

Solid compositions of a similar type may also be employed as fillers in gelatin or HPMC capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the formula (I) may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerol, and combinations thereof.

The compounds of the formula (I) can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion or needleless injection techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art. For oral or parenteral administration to human patients the daily dosage levels of compounds of formula (I), and their pharmaceutically acceptable salts, will be from 0.01 to 30 mg/kg (in single or divided doses) and preferably will be in the range 0.01 to 15 mg/kg. Thus tablets will contain 1 mg to 0.5 g of compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

Oral administration is preferred. Preferably, administration takes place shortly before an effect is required.

The compounds of formula (I) can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or

nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the formula (I) and a suitable powder base such as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 µg to 10 mg of a compound of the formula (I) for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 1 µg to 20 mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

Alternatively, the compounds of the formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compounds of the formula (I) may also be dermally or transdermally administered, for example, by the use of a skin patch. They may also be administered by the pulmonary or rectal routes.

They may also be administered by the ocular route, particularly for treating inflammatory conditions or diseases of the eye. For ophthalmic use, the compounds can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

For application topically to the skin, the compounds of the formula (I) can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds of the formula (I) may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

The compounds of formula (I), and their pharmaceutically acceptable salts, have the advantage that they are more selective, have a more rapid onset of action, are more potent, are more stable, are more resistant to metabolism, or have other more desirable properties than the compounds of the prior art.

Included within the scope of the present invention are emulsions comprising coadministration of, and compositions which contain, in addition to a compound of the

present invention as active ingredient, additional therapeutic agents and active ingredients. Such multiple drug regimens, often referred to as combination therapy, may be used in the treatment and prevention of any of the diseases or conditions mediated by or associated with CCR5 chemokine receptor modulation, particularly infection by human immunodeficiency virus, HIV. The use of such combinations of therapeutic agents is especially pertinent with respect to the treatment and prevention of infection and multiplication of the human immunodeficiency virus, HIV, and related pathogenic retroviruses within a patient in need of treatment or one at risk of becoming such a patient. The ability of such retroviral pathogens to evolve within a relatively short period of time into strains resistant to any monotherapy which has been administered to said patient is well known in the literature.

In addition to the requirement of therapeutic efficacy which may necessitate the use of active agents in addition to the CCR5 chemokine receptor modulating compounds of formula (I), and their pharmaceutically acceptable salts, there may be additional rationales which compel or highly recommend the use of combinations of drugs involving active ingredients which represent adjunct therapy, i.e., which complement and supplement the function performed by the CCR5 chemokine receptor modulating compounds of the present invention. Such supplementary therapeutic agents used for the purpose of auxiliary treatment include drugs which, instead of directly treating or preventing a disease or condition mediated by or associated with CCR5 chemokine receptor modulation, treat diseases or conditions which directly result from or indirectly accompany the basic or underlying CCR5 chemokine receptor modulated disease or condition. For example, where the basic CCR5 chemokine receptor modulated disease or condition is HIV infection and multiplication, it may be necessary or at least desirable to treat opportunistic infections, neoplasms, and other conditions which occur as the result of the immunocompromised state of the patient being treated. Other active agents may be used with the compounds of formula (I), and their pharmaceutically acceptable salts, e.g., in order to provide immune stimulation or to treat pain and inflammation which accompany the initial and fundamental HIV infection.

Thus, the methods of treatment and pharmaceutical compositions of the present invention may employ the compounds of formula (I), and their pharmaceutically acceptable salts, in the form of monotherapy, but said methods and compositions may also be used in the form of multiple therapy in which one or more compounds of formula (I), or their pharmaceutically acceptable salts, are coadministered in combination with one or more known therapeutic agents such as those described in detail further herein.

Preferred combinations of the present invention include simultaneous, or sequential treatments with a compound of formula (I), or a pharmaceutically acceptable salt thereof, and one or more inhibitors of HIV protease and/or inhibitors of HIV reverse transcriptase, preferably selected from the class of non-nucleoside reverse transcriptase inhibitors (NNRTI), including but not limited to nevirapine, delavirdine and efavirenz; from among the nucleoside/nucleotide inhibitors, including but not limited to zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, adefovir and dipivoxil; and from among the protease inhibitors, including but not limited to indinavir, ritonavir, saquinavir, nelfinavir, lopinavir and amprenavir. Other agents useful in the above-described preferred emulsion combinations of the present invention include current and

to-be-discovered investigational drugs from any of the above classes of inhibitors, including but not limited to FTC, PMPA, fozivudine tidozil, talviraline, S-1153, MKC442, MSC-204, MSH-372, DMP450, PNU-140690, ABT-378 and KNI-764. There is also included within the scope of the preferred embodiments of the present invention, combinations of a compound of formula (I), or a pharmaceutically acceptable salt thereof, together with a supplementary therapeutic agent used for the purpose of auxiliary treatment, wherein said supplementary therapeutic agent comprises one or more members independently selected from the group consisting of proliferation inhibitors, e.g., hydroxyurea; immunomodulators, e.g., sargramostim, and various forms of interferon or interferon derivatives; fusion inhibitors, e.g., AMD3100, T-20, PRO-542, AD-349, BB-10010 and other chemokine receptor agonists/antagonists; tachykinin receptor modulators, e.g. NK1 antagonists; integrase inhibitors, e.g., AR177; RNaseH inhibitors; inhibitors of viral transcription and RNA replication; and other agents that inhibit viral infection or improve the condition or outcome of HIV-infected individuals through different mechanisms.

Preferred methods of treatment of the present invention for the prevention of HIV infection, or treatment of aviremic and asymptomatic subjects potentially or effectively infected with HIV, include but are not limited to administration of a member independently selected from the group consisting of: (i) a compound within the scope of formula (I) as disclosed herein; (ii) one NNRTI in addition to a compound of (i); (iii) two NRTI in addition to a compound of (i); (iv) one NRTI in addition to the combination of (ii); and (v) a compound selected from the class of protease inhibitors used in place of a NRTI in combinations (iii) and (iv).

The preferred methods of the present invention for therapy of HIV-infected individuals with detectable viremia or abnormally low CD4 counts further include as a member to be selected: (vi) treatment according to (i) above in addition to the standard recommended initial regimens for the therapy of established HIV infections, e.g., see <http://hivatis.org/trtgdlns.html>. Such standard regimens include but are not limited to an agent from the class of protease inhibitors in combination with two NRTIs; and (vii) a standard recommended initial regimens for the therapy of established HIV infections, e.g., see <http://hivatis.org/trtgdlns.html>, where either the protease inhibitor component, or one or both of the NRTIs is/are replaced by a compound within the scope of formula (I) as disclosed herein.

The preferred methods of the present invention for therapy of HIV-infected individuals that have failed antiviral therapy further include as a member to be selected: (viii) treatment according to (i) above, in addition to the standard recommended regimens for the therapy of such patients, e.g., see <http://hivatis.org/trtgdlns.html>; and (ix) a standard recommended initial regimens for the therapy of patients who have failed antiretroviral therapy, e.g., see <http://hivatis.org/trtgdlns.html>, where either one of the protease inhibitor components, or one of both of the NRTIs is/are replaced by a compound within the scope of formula (I) as disclosed herein.

In the above-described preferred embodiment combinations of the present invention, the compound of formula (I) and other therapeutic active agents may be administered in terms of dosage forms either separately or in conjunction with each other, and in terms of their time of administration, either serially or simultaneously. Thus, the administration of one component agent may be prior to, concurrent with, or subsequent to the administration of the other component agent(s).

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

Thus the invention provides:

a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;

processes for the preparation of a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;

a pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;

a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;

a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for the treatment of a disorder in which the modulation of CCR5 receptors is implicated;

a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for the treatment of HIV, a retroviral infection genetically related to HIV, AIDS, or an inflammatory disease;

a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for the treatment of a respiratory disorder including adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis or chronic sinusitis;

a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for the treatment of an inflammatory bowel disease, including Crohn's disease or ulcerative colitis, multiple sclerosis, rheumatoid arthritis, graft rejection, including a kidney or a lung allograft, endometriosis, type I diabetes, a renal disease, chronic pancreatitis, an inflammatory lung condition or chronic heart failure;

the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of a disorder in which the modulation of CCR5 receptors is implicated;

the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of HIV, a retroviral infection genetically related to HIV, AIDS, or an inflammatory disease;

the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of a respiratory disorder including adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis or chronic sinusitis; the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of an inflammatory bowel disease, including Crohn's disease or ulcerative colitis, multiple sclerosis, rheumatoid arthritis, graft rejection, including a kidney or a lung allograft, endometriosis, type I diabetes, a renal disease, chronic pancreatitis, an inflammatory lung condition or chronic heart failure;

a method of treatment of a mammal to treat a disorder in which the modulation of CCR5 receptors is implicated including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

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a method of treatment of a mammal to treat HIV, a retroviral infection geotically related to HIV, AIDS, or an inflammatory disease including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

a method of treatment of a mammal to treat a respiratory disorder including adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis or chronic sinusitis including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

a method of treatment of a mammal to treat an inflammatory bowel disease, including Crohn's disease or ulcerative colitis, multiple sclerosis, rheumatoid arthritis, graft rejection, including a kidney or a lung allograft, endometriosis, type 1 diabetes, a renal disease, chronic pancreatitis, an inflammatory lung condition or chronic heart failure including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof; and

intermediates of the formulae (II), (IIA), (VII), (VIA), (XII), (XIV), (XVIII) and (XIX).

The invention is illustrated by the following Examples, in which the following abbreviations may be used:

0.88 ammonia=concentrated ammonium hydroxide solution, 0.88 SG

h=hour

min=minute

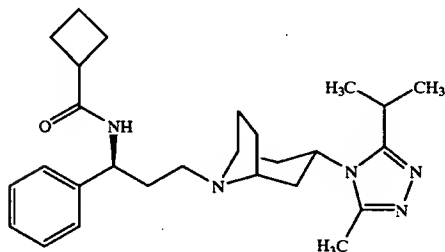
MS=mass spectrum

NMR=nuclear magnetic resonance

Me=methyl

EXAMPLE 1

N-((1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)cyclobutancarboxamide



N-Boc-3-((1S)-3-[3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-L-proline (1.15 g, 0.88 mmol) was added to a solution of the title compound from Preparation 11 (250 mg, 0.68 mmol) and cyclobutancarboxylic acid (130 μ l, 1.37 mmol) in dichloromethane (10 ml) and the mixture stirred at room temperature for 16 hours. The mixture was filtered through Celite® (filtration aid) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol: 0.88 ammonia (1:0:0 to 95:5:0.5, by volume) to afford the title compound as a white foam, 200 mg.

Found C, 69.98; H, 8.67; N, 14.89%

$C_{27}H_{39}N_5O$; 0.2 CH_2Cl_2 ; requires C, 70.01; H, 8.51; N, 15.01%

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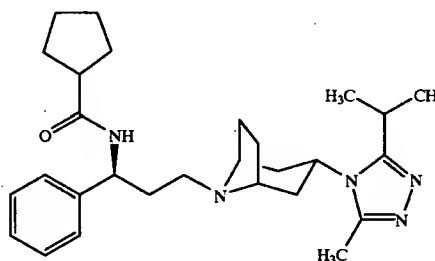
1H -NMR (400 MHz, $CDCl_3$): δ [ppm] 1.40 (6H, d), 1.63 (4H, m), 1.85–2.45 (14H, m), 2.52 (3H, s), 3.00 (2H, m), 3.39 (2H, m), 4.30 (1H, m), 5.15 (1H, m), 6.35 (1H, m), 7.15–7.40 (5H, m).

LRMS: m/z 450.3 (MH^+)

$[\alpha]_D^{25} -34.0^\circ$ (c=0.10, MeOH)

EXAMPLE 2

N-((1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)cyclohexancarboxamide



Cyclohexancarboxylic acid (115 μ l, 1.06 mmol) was added to a solution of the title compound from Preparation 11 (300 mg, 0.82 mmol), hydroxybenzotriazole hydrate (10 mg, 74 μ mol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide (300 mg, 1.07 mmol) in dichloromethane (10 ml) and the mixture stirred at room temperature for 3 hours. Saturated aqueous sodium carbonate solution (50 ml) was added to the mixture and the product was extracted with dichloromethane (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol: 0.88 ammonia (1:0:0 to 96:4:0.4, by volume) to afford the title compound as a white foam, 330 mg.

Found C, 69.73; H, 9.00; N, 14.09% $C_{28}H_{41}N_5O$; 0.25 CH_2Cl_2 ; requires C, 69.98; H, 8.63; N, 14.44%.

1H -NMR (400 MHz, $CDCl_3$): δ [ppm] 1.35 (6H, d), 1.51–2.04 (16H, m), 2.17 (2H, m), 2.39 (2H, m), 2.45 (4H, m), 2.95 (1H, m), 3.36 (2H, s), 4.25 (1H, m), 5.09 (1H, m), 6.12 (1H, m), 7.20–7.33 (5H, m).

LRMS: m/z 464.8 (MH^+)

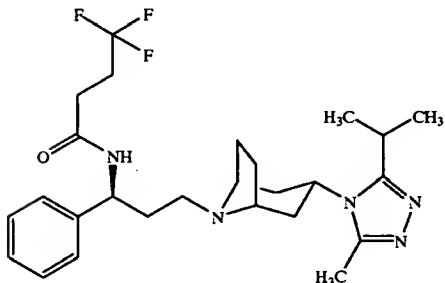
$[\alpha]_D^{25} -29.21^\circ$ (c=0.10, MeOH)

Melting point [$^\circ C$]: 68–70

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EXAMPLE 3

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-4,4,4-trifluorobutanamide



N-Benzyl-N'-cyclohexylcarbodiimide-polymer bound (370 mg, 0.336 mmol) was added to a solution of the title compound from Preparation 11 (100 mg, 0.27 mmol) and 4,4,4-trifluorobutanecarboxylic acid (45 mg, 0.32 mmol) in dichloromethane (4 ml) and the mixture was stirred at room temperature for 1.5 hours. The mixture was filtered through Celite® and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol: 0.88 ammonia (1:0:0 to 95:5:0.5, by volume) to afford the title compound as a white foam, 75 mg.

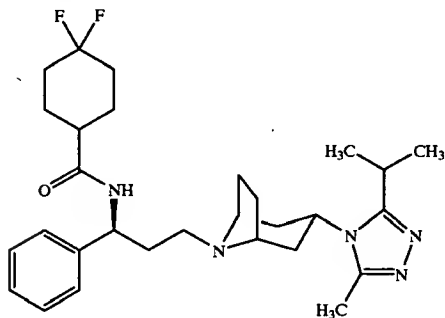
Found C, 61.55; H, 7.46; N, 13.62% $C_{26}H_{36}N_5OF_3 \cdot 0.25 CH_2Cl_2$; requires C, 61.48; H, 7.17; N, 13.66%

1H -NMR (400 MHz, $CDCl_3$): δ [ppm] 1.39 (6H, d), 1.65 (5H, m), 1.98 (2H, m), 2.07 (2H, m), 2.15–2.29 (2H, m), 2.43 (5H, m), 2.52 (3H, s), 3.00 (1H, m), 3.40 (2H, s), 4.30 (1H, m), 5.15 (1H, m), 6.94 (1H, m), 7.28 (3H, m), 7.36 (2H, m)

LRMS: m/z 492.3 (MH^+)
 $[\alpha]_D^{25} -32.41^\circ$ (c=0.10, MeOH)

EXAMPLE 4

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-4,4-difluorocyclohexanecarboxamide



N-Benzyl-N'-cyclohexylcarbodiimide-polymer bound (500 mg, 0.545 mmol) was added to a solution of the title compound from Preparation 11 (100 mg, 0.27 mmol) and 4,4-difluorocyclohexanecarboxylic acid (50 mg, 0.30 mmol) in dichloromethane (4 ml) and the mixture was stirred at room temperature for 1.5 hours. The mixture was filtered through Celite® and evaporated under reduced pressure. The residue was purified by column chromatography on

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silica gel using an elution gradient of dichloromethane: methanol: 0.88 ammonia (1:0:0 to 95:5:0.5, by volume) to afford the title compound as a white foam, 67 mg.

Found C, 64.68; H, 7.88; N, 12.65% $C_{29}H_{41}N_5OF_2 \cdot 1.36 H_2O$; requires C, 64.72; H, 8.19; N, 13.01%

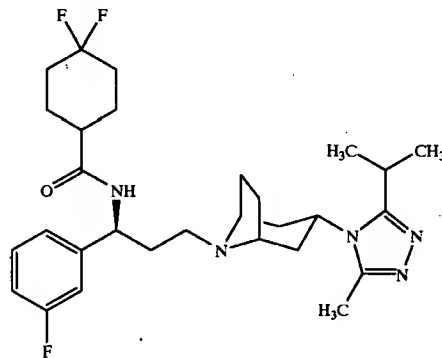
1H -NMR (400 MHz, $CDCl_3$): δ [ppm] 1.39 (6H, d), 1.61–2.18 (19H, m), 2.28 (2H, m), 2.48 (3H, s), 2.85 (1H, m), 3.36 (2H, br d), 4.28 (1H, m), 5.15 (1H, m), 6.48–6.61 (1H, br m), 7.23 (3H, m), 7.36 (2H, m)

LRMS: m/z 514.4 (MH^+)

PXRD analysis showed the product to be a mixture of polymorphs termed "Form A" and "Form B". Single crystals of pure Form A and Form B could be identified and separated from the mixture. The PXRD data for Forms A and B are listed in Appendix 1.

EXAMPLE 5

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl}-4,4-difluorocyclohexanecarboxamide



The title compound was prepared from the title compound from Preparation 13 (200 mg, 0.52 mmol) and 4,4-difluorocyclohexanecarboxylic acid (128 mg, 0.79 mmol) using a similar method to that described in Example 4, 160 mg.

Found C, 64.25; H, 7.67; N, 12.53%

$C_{29}H_{40}N_5OF_3 \cdot 0.7 H_2O$; requires C, 64.00; H, 7.67; N, 12.87%

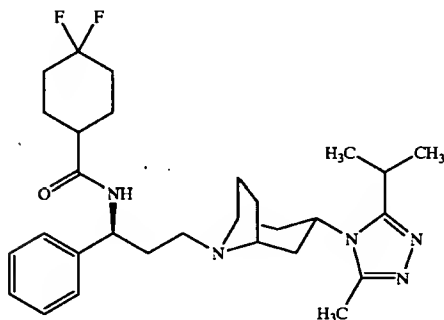
1H -NMR (400 MHz, $CDCl_3$): δ [ppm] 1.39 (6H, d), 1.60–2.35 (19H, m), 2.42–2.60 (2H, m), 2.55 (3H, s), 2.98 (1H, m), 3.40 (2H, br d), 4.32 (1H, m), 5.14 (1H, m), 6.79 (1H, br m), 6.97 (2H, m), 7.05 (1H, m), 7.31 (1H, m).

LRMS: m/z 532 (MH^+).

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EXAMPLE 6

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-4,4-difluorocyclohexanecarboxamide



The title compound from Preparation 20 (176 g, 0.48 mol) was dissolved in dichloromethane (1.76 l). A solution of saturated aqueous sodium carbonate (1.76 l) and water (1.76 l) was added. An exotherm was observed and the mixture was cooled to 15° C. A solution of the title compound from Preparation 14 (131.6 g, 0.72 mol) in toluene (500 ml) was added to the reaction mixture and an exotherm was observed. The resultant mixture was stirred for 12 h at room temperature. HPLC analysis of the reaction mixture indicated that the reaction had reached completion. Water (1 l) and dichloromethane (1 l) were added to facilitate phase separation. The phases were separated and pH of the aqueous phase was pH=11. The aqueous phase was washed with dichloromethane (1.76 l). The combined organic phases were washed with 0.5 M aqueous sodium hydroxide (1.76 l) and then with water (1.76 l). The organic phase was concentrated and ethyl acetate (700 ml) added. The mixture was allowed to granulate at ambient temperature over night. The white solid was filtered off and the product was washed with ethyl acetate (60 ml) and dried in a vacuum oven for 12 h at 40° C. to give the title compound as a white solid 146 g (59%).

¹H-NMR was identical to the title compound in Example 4.

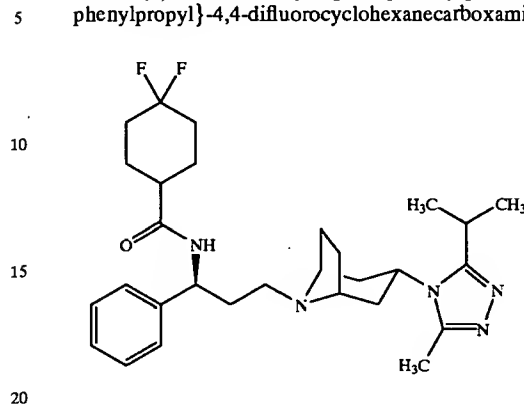
PXRD analysis showed the product to be a single polymorph termed "Form B". The PXRD data for Form B are listed in Appendix 1.

The melting point of Form B was determined as 197° C. (peak temperature) using a T.A. Instruments 2100 DSC. The Scan was made at 20° C./minute, (ambient to 300° C.) with nitrogen flow gas.

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EXAMPLE 7

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-4,4-difluorocyclohexanecarboxamide

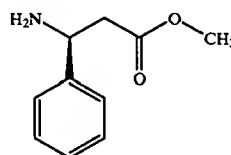


The title compound from Preparation 9 was slurried in dichloromethane (9 ml) and a solution of the title compound from Preparation 17 (1.58 g, 5.35 mmol) in toluene (3.2 ml) was added to the reaction mixture followed by addition of acetic acid (0.3 ml). To the resultant solution was added sodium triacetoxyborohydride (1.36 g, 6.24 mmol) in portions. The resultant slurry was stirred at room temperature for 30 minutes. A sample was analysed by HPLC and TLC and the reaction was deemed complete. Water (10 ml) was added followed by 2 M aqueous potassium hydroxide solution (10 ml) and the layers were separated. The aqueous phase was washed with dichloromethane (10 ml) and the combined organic layers were washed with 1 M aqueous potassium hydroxide solution (10 ml). The organic layer was concentrated under reduced pressure to yield a pale brown foam which was reslurried in ethyl acetate (10 ml) for 12 hours at room temperature. The white solid was filtered off and dried in an oven under reduced pressure at 40° C. for 4 hours to give the title compound which is identical with the title compound from Example 4, 2.05 g, 75% yield.

The following Preparations illustrate the preparation of certain intermediates used in the above Examples.

Preparation 1

Methyl (3S)-3-amino-3-phenylpropanoate



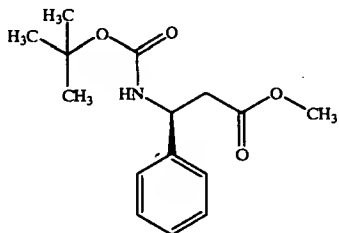
A solution of tert-butyl (3S)-3-amino-3-phenylpropanoate (5.04 g, 22.9 mmol) in 2.25 M methanolic hydrogen chloride (100 ml) was heated under reflux for 2½ hours. The mixture was cooled to room temperature, basified with saturated aqueous sodium carbonate solution to pH 8 and the phases separated. The aqueous layer was extracted with dichloromethane (4x). The combined organic solutions were washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound, 3.97 g.

¹H-NMR (400MHz, CDCl₃): δ [ppm] 1.70 (2H, s), 2.66 (2H, d), 3.68 (3H, s), 4.43 (1H, t), 7.25–7.40 (5H, m). LRMS: m/z 180.3 (MH⁺).

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Preparation 2

Methyl (3S)-3-[(tert-butoxycarbonyl)amino]-3-phenylpropanoate



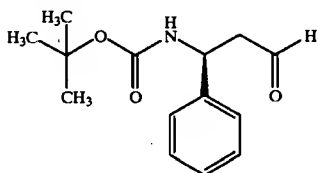
A mixture of the title compound from Preparation 1 (5.38 g, 30 mmol), di-tert-butyl dicarbonate (8.72 g, 40 mmol), tetrahydrofuran (50 ml) and 2N aqueous sodium hydroxide solution (25 ml) were stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate, the layers separated and the aqueous phase extracted with ethyl acetate (2x). The combined organic solutions were washed with water, brine, dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as a white solid, 8.39 g.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.41 (9H, s), 2.84 (2H, m), 3.61 (3H, s), 5.10 (1H, bs), 5.41 (1H, bs), 7.22–7.36 (5H, m).

LRMS: m/z 279.7 (MH⁺)

Preparation 3

tert-Butyl (1S)-3-oxo-1-phenylpropylcarbamate



Diisobutylaluminum hydride (1 M in dichloromethane, 60 ml, 60 mmol) was cooled to -78° C. and added dropwise to a solution of the title compound from Preparation 2 (8.39 g, 30 mmol) in dichloromethane (150 ml) at -78° C. The reaction was stirred for 90 minutes then methanol (pre-cooled to -78° C., 40 ml) was added. The mixture was allowed to warm to room temperature and poured into 2 M aqueous hydrochloric acid (200 ml). The layers were separated and the aqueous phase extracted with dichloromethane (2x). The combined organic layers were dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as a white solid, 6.72 g.

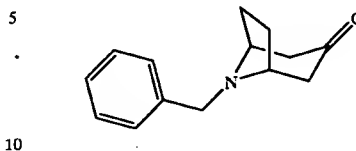
¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.42 (9H, s), 2.86–3.00 (2H, m), 5.06 (1H, bs), 5.20 (1H, bs), 7.22–7.38 (5H, m), 9.75 (1H, s).

LRMS: m/z 250.1 (MH³⁰).

26

Preparation 4

8-Benzyl-8-azabicyclo[3.2.1]octan-3-one



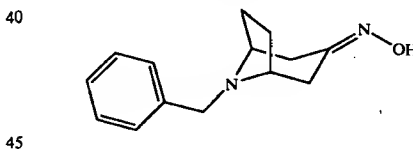
A solution of 2,5-dimethoxytetrahydrofuran (50 g, 378 mmol) in 0.025 M aqueous hydrochloric acid (160 ml) was cooled to 0° C. and stirred for 16 hours. Benzylamine hydrochloride (65 g, 453 mmol), ketomalonic acid (55 g, 377 mmol) and an aqueous solution of sodium acetate (300 ml, 0.69 M) were added and the reaction stirred at room temperature for 1 hour. The mixture was heated to 50° C. for a further 90 minutes then cooled in an ice bath and basified to pH12 with 2 N aqueous sodium hydroxide solution. The layers were separated, and the aqueous phase extracted with ethyl acetate (3x). The combined organic solutions were washed with water, dried (MgSO₄), filtered and evaporated under reduced pressure. The residual brown oil was distilled under reduced pressure (126° C./0.4 kPa) to afford the title compound as an off-white solid, 37.81 g.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.64 (2H, m), 2.06–2.14 (2H, m), 2.18 (1H, s), 2.23 (1H, s), 2.68 (1H, m), 2.72 (1H, m), 3.48 (2H, s), 3.73 (2H, s), 7.20–7.29 (1H, m), 7.32 (2H, m), 7.42 (2H, d).

LRMS: m/z 216.3 (MH⁺)

Preparation 5

8-Benzyl-8-azabicyclo[3.2.1]octan-3-one oxime



A mixture of the title compound from Preparation 4 (17.72 g, 82 mmol), hydroxylamine hydrochloride (5.72 g, 82 mmol) and pyridine (7.2 ml, 89 mmol), was heated under reflux in ethanol (500 ml) for 20 hours. The reaction was allowed to cool to room temperature and diluted with saturated aqueous sodium carbonate solution. The mixture was filtered and the filtrate evaporated under reduced pressure. The residue was partitioned between dichloromethane and water, the layers separated and the aqueous layer extracted with dichloromethane (2x). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as a pale brown solid, 18.10 g.

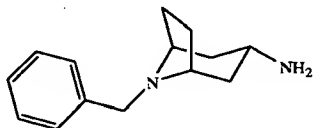
¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.45–1.56 (1H, m), 1.60–1.67 (1H, m), 1.96–2.07 (2H, bm), 2.12 (1H, m), 2.21 (1H, m), 2.57 (1H, m), 2.97 (1H, m), 3.32 (2H, m), 3.64 (2H, s), 7.06 (1H, s), 7.21–7.28 (1H, m), 7.32 (2H, m), 7.38 (2H, d).

LRMS: m/z 231.2 (MH⁺)

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Preparation 6

8-Benzyl-8-azabicyclo[3.2.1]octan-3-exo-amine



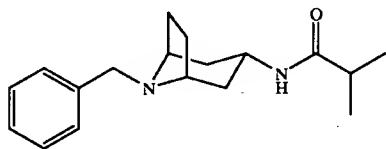
A solution of the title compound from Preparation 5 (18.10 g, 79 mmol) in pentanol (500 ml) was heated under reflux. Sodium (22.0 g, 957 mmol) was added portionwise over 2.5 hours. The reaction was then heated under reflux for a further 2 hours then cooled to 0° C. in an ice bath. Water was added until no more hydrogen gas was evolved. The mixture was acidified using 6 N aqueous hydrochloric acid and the phases separated. The organic layer was extracted with 6 N aqueous hydrochloric acid (3x), the combined aqueous extracts were basified to pH 12 with sodium hydroxide pellets (400 g) and the aqueous solution extracted with ethyl acetate (3x). The combined organic solutions were dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound, 15.65 g.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.20–1.40 (2H, hm), 1.48 (2H, m), 1.58 (2H, d), 1.64–1.76 (2H, hm), 2.00 (2H, hm), 2.95 (1H, m), 3.19 (2H, hs), 3.57 (2H, s), 7.18–7.26 (1H, m), 7.30 (2H, m), 7.37 (2H, d).

LRMS: m/z 217.3 (MH⁺).

Preparation 7

N-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-yl-exo)-2-methylpropanamide



Triethylamine (9 ml, 66.8 mmol) was added to a solution of the title compound from Preparation 6 (13 g, 60.1 mmol), isohutyric acid (5.6 ml, 60.5 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.6 g, 60.4 mmol) in dichloromethane (150 ml). The reaction mixture was stirred at room temperature for 3 hours after which time isohutyric acid (1.4 ml, 15 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.9 g, 15.1 mmol) were added. The reaction mixture was stirred at room temperature for 2 days after which time isohutyric acid (2.6 ml, 28 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5 g, 26 mmol) and triethylamine (3 ml, 22.3 mmol) were added. The reaction was stirred for 24 hours. Saturated aqueous sodium carbonate solution (300 ml) was added to the mixture and the product was extracted with dichloromethane (2x). The combined organic layers were washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol: 0.88 ammonia (1:0:0 to 97:3:0.3, by volume) to afford the title compound as a white powder, 9.2 g.

Found C, 75.43; H, 9.30; N, 9.82% C₁₈H₂₆N₂O requires C, 75.48; H, 9.15; N, 9.78%

¹H-NMR (400 MHz, CDCl₃): δ [ppm] 1.10 (6H, d), 1.47 (2H, tr), 1.60 (2H, s), 1.70 (2H, m), 1.80 (2H, m), 2.02 (2H,

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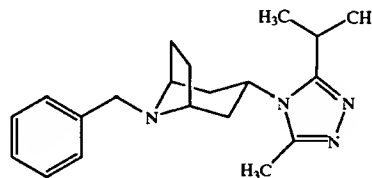
m), 2.27 (1H, m), 3.20 (2H, s), 4.10 (1H, m), 5.15 (1H, m), 7.20–7.40 (5H, m).

LRMS: m/z 287.4 (MH⁺)

Melting point [° C.]: 138–140

Preparation 8

8-Benzyl-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]octane



Phosphorus oxychloride (9 ml, 96.9 mmol) was added to a solution of the title compound from Preparation 7 (9.2 g, 32 mmol) and pyridine (16 ml, 196 mmol) in chloroform (20 ml) at 0° C. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 5 hours. The mixture was evaporated under reduced pressure. The residue was dissolved in chloroform (40 ml) and acetic hydrazide (3.6 g, 48.6 mmol) was added. The mixture was heated under reflux for 3 hours. Saturated aqueous sodium carbonate solution (250 ml) was added to the mixture and the product was extracted with dichloromethane (2x). The combined organic layers were washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure. Toluene (200 ml) and p-toluenesulphonic acid monohydrate (100 mg, 0.53 mmol) were added to the residue. The reaction mixture was heated under reflux for 2 hours. The reaction mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol: 0.88 ammonia (1:0:0 to 95:5:0.5, by volume) to afford the crude product. The crude material was suspended in 6N aqueous hydrochloric acid (40 ml) and heated under reflux for 12 hours after which time 12 N aqueous hydrochloric acid (4 ml) was added. The reaction mixture was heated under reflux for 2 hours. The mixture was evaporated under reduced pressure. The residue was basified by the addition of saturated aqueous potassium carbonate solution (200 ml) and the product was extracted with dichloromethane (3x). The combined organic layers were washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol: 0.88 ammonia (1:0:0 to 96:4:0.4, by volume) to afford the title compound as a white powder, 3.12 g.

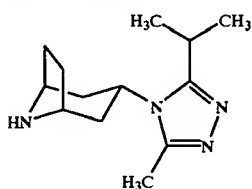
¹H-NMR (300 MHz, CDCl₃): α [ppm] 1.40 (6H, d), 1.70 (4H, m), 2.15–2.40 (4H, m), 2.60 (3H, s), 3.07 (1H, m), 3.37 (2H, s), 3.60 (2H, s), 4.30 (1H, m), 7.25–7.40 (5H, m).

LRMS: m/z 325.3 (MH⁺)

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Preparation 9

3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]octane



Ammonium formate (6 g, 92 mmol) was added to a solution of the title compound from Preparation 8 (3.12 g, 9.6 mmol) and palladium (II) hydroxide (500 mg) in ethanol (400 ml). The mixture was heated under reflux for 2 hours after which time 0.88 ammonia solution (2 ml) was added. The mixture was heated under reflux for 1 hour and the reaction was allowed to cool to room temperature and filtered through Arbocel™ (filtration aid). The solvent was evaporated under reduced pressure to afford the title compound as a white solid, 1.91 g

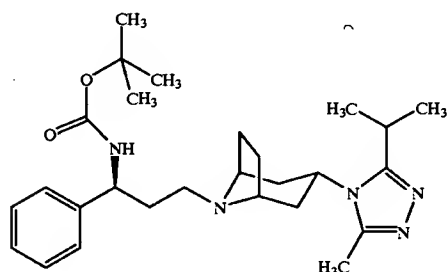
¹H-NMR (300 MHz, CDCl₃): δ [ppm] 1.37 (6H, d), 1.70–2.25 (8H, m), 2.50 (3H, s), 3.05 (1H, m), 3.70 (2H, m), 4.32 (1H, m).

LRMS: m/z 235.0(MH⁺)

Melting point [° C.]: 150–154

Preparation 10

tert-Butyl (1S)-3-[3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropylcarbamate



Sodium triacetoxyborohydride (1.7 g, 8.02 mmol) and glacial acetic acid (1 ml, 17.5 mmol) were added to a solution of the title compound from Preparation 9 (1.6 g, 6.84 mmol) and the title compound from Preparation 3 (2 g, 8.03 mmol) in dichloromethane (40 ml) and the reaction stirred at room temperature for 2 hours. The mixture was basified with 10% w/w aqueous potassium carbonate solution and extracted with dichloromethane (2x). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol: 0.88 ammonia (1:0:0 to 97.5:2.5:0.25, by volume) to afford the title compound as a white foam, 2.5 g

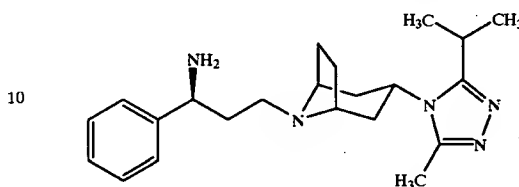
¹H-NMR (300 MHz, CDCl₃): δ [ppm] 1.40 (15H, m), 1.70 (4H, m), 1.80–2.15 (4H, m), 2.30 (2H, m), 2.40 (2H, m), 2.58 (3H, s), 3.00 (1H, m), 3.40 (2H, m), 4.30 (1H, m), 4.85 (1H, m), 6.20 (1H, m), 7.20–7.40 (5H, m).

LRMS: m/z 468.4 (MH⁺)

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Preparation 11

(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenyl-1-propanamine



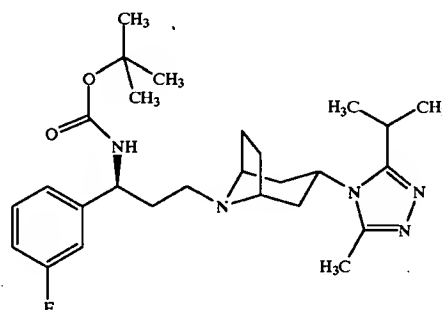
A mixture of the title compound from Preparation 10 (2.5 g, 5.35 mmol), 2.25 M aqueous hydrochloric acid and methanol (70 ml) was heated under reflux for 5 minutes and stirred at room temperature for 1.5 hours. The reaction mixture was allowed to cool to room temperature and evaporated under reduced pressure. The residue was basified by the addition of saturated aqueous sodium carbonate solution (150 ml) and extracted with dichloromethane (2x). The combined organic layers were washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as a white foam, 1.80 g.

¹H-NMR (400 MHz, CDCl₃): δ [ppm] 1.37 (6H, m), 1.42 (4H, m), 1.85 (2H, m), 2.05 (2H, m), 2.20 (2H, m), 2.42 (5H, m), 3.00 (1H, m), 3.37 (2H, m), 4.10 (1H, m), 4.30 (1H, m), 7.30 (5H, m).

[α]_D²⁰ +15.0° (c=0.10, MeOH)

Preparation 12

tert-Butyl (1S)-3-[3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propylcarbamate



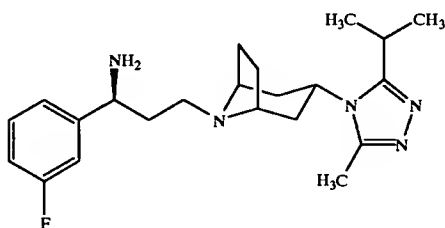
The title compound was prepared from the title compound from Preparation 9 (1.0 g, 4.27 mmol) and tert-butyl (1S)-3-oxo-1-(3-fluorophenyl)propylcarbamate (EP-A-1013276) (2.2 g, 8.23 mmol) using a similar method to that described in Preparation 10, 0.76 g.

LRMS: m/z 486 (MH⁺).

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Preparation 13

(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)-1-propanamine

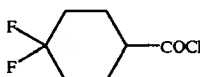


The title compound was prepared from the title compound from Preparation 12 (760 mg, 1.57 mmol) using a similar method to that described in Preparation 11, 200 mg.

LRMS: m/z 386.2 (M^+).

Preparation 14

4,4-Difluorocyclohexanecarbonyl chloride

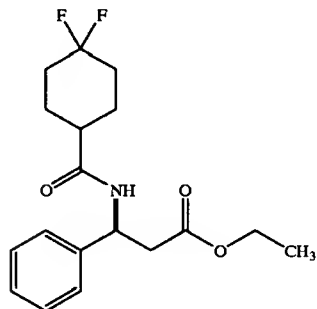


4,4-Difluorocyclohexanecarboxylic acid (118.2 g, 0.72 mol) was dissolved in toluene (296 ml). To the clear solution was added thionyl chloride (261 ml, 3.6 mol) and the resultant solution was heated under reflux for 1.5 hours. A sample was taken and concentrated and $^1\text{H-NMR}$ indicated complete conversion to the title compound. The reaction was cooled to room temperature and the thionyl chloride was removed under reduced pressure and replaced with toluene to give the title compound as a toluene concentrate at a total volume of 591 ml.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ [ppm] 2.29 (1H, m), 2.20–1.70 (8H, m).

Preparation 15

Ethyl (3S)-3-[[[(4,4-difluorocyclohexyl)carbonyl]amino]-3-phenylpropanoate



Ethyl (3S)-3-amino-3-phenylpropanoate hydrochloride (10 g, 43.6 mmol) was slurried in dichloromethane (100 ml) and a saturated aqueous solution of sodium carbonate (100 ml) and water (100 ml) added. The mixture was cooled to 0°C . and solution of the title compound from Preparation 14 (7.96 g, 43.6 mmol) in toluene (38 ml) was added to the reaction mixture. The resultant mixture was stirred for 1 hour at room temperature. HPLC analysis of the reaction mixture indi-

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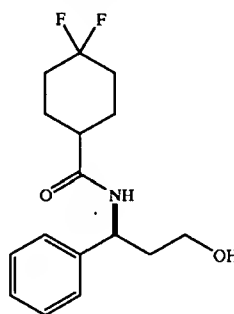
cated that the reaction had reached completion. The layers were separated. The pH of the aqueous phase was $\text{pH}=9$. The aqueous layer was washed with dichloromethane (100 ml). The combined organic layers were washed with water (100 ml) and then with 1 M aqueous hydrochloric acid (100 ml) followed by a wash with water (100 ml). The organic layer was concentrated to a brown oil and the oil was granulated in ethyl acetate: heptane 1:2, by volume (50 ml) for 4 hours. The white solid was filtered off and dried in an oven under reduced pressure for 12 hours at 40°C . to yield the title compound as a white solid, 10.9 g, 66% in yield.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ [ppm] 7.30 (5H, m), 6.76 (1H, br d), 5.40 (1H, m), 4.08 (2H, q), 2.95–2.75 (2H, m), 2.30–1.65 (9H, m), 1.15 (3H, t).

LRMS: $m/z=338$ (M^+)

Preparation 16

(1S)-4,4-Difluoro-N-(3-hydroxy-1-phenylpropyl)cyclohexanecarboxamide



(3S)-3-Amino-3-phenylpropanol (30.9 g, 0.20 mol) was dissolved in dichloromethane (300 ml) and aqueous saturated sodium carbonate solution (300 ml) was added. The resultant biphasic mixture was cooled to 5°C . and the title compound from Preparation 14 was added as a toluene concentrate (37.3 g, 0.20 mol, 224 ml), keeping the temperature below 10°C . The resultant slurry was stirred for 15 minutes at 5°C . HPLC analysis of a sample indicated that the reaction had gone to completion. Water (310 ml) was added and a biphasic mixture was obtained. The layers were separated, the aqueous layer was washed with dichloromethane (300 ml) and the combined organic layers were washed with 1 M aqueous sodium hydroxide solution (300 ml). The combined organic layers were concentrated under reduced pressure to a brown solid. The solid was slurried in toluene (120 ml) which resulted in a thick white slurry. Methyl-tert-butyl ether (240 ml) was added to give a mobile white slurry. The slurry was stirred at 0°C . for 1 hour and the white solid was filtered off. The solid was dried in an oven under reduced pressure for 12 hours at 40°C . to give the title compound, 53.9 g, 89% yield.

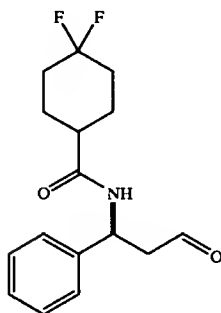
$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ [ppm] 7.30 (5H, m), 6.18 (1H, br d), 5.20 (1H, m), 3.75–3.50 (2H, m), 3.05 (1H, br s), 2.18 (4H, m), 2.00–1.62 (7H, m).

LRMS: $m/z=297$ (M^+)

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Preparation 17

(1S)-4,4-Difluoro-N-(3-oxo-1-phenylpropyl) cyclohexanecarboxamide



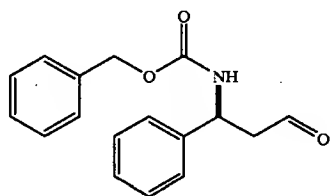
Sulphur trioxide pyridine complex (80.3 g, 0.50 mol) was slurried in dichloromethane (175 ml) under an atmosphere of nitrogen. Dimethylsulfoxide (175 ml) was added and the resultant solution was cooled to 0° C. A solution of the compound from Preparation 16, triethylamine (70 ml, 0.50 mol) and dimethylsulfoxide (88 ml) in dichloromethane (88 ml) was added slowly to the reaction mixture keeping the temperature below 10° C. The resultant yellow solution was stirred at 0° C. for 2 hours until a TLC sample indicated that all starting material was consumed. Water (750 ml) was added and a biphasic mixture was obtained. The mixture was diluted with toluene (750 ml) and the layers were separated. The organic layer was washed with 0.5 M aqueous hydrochloric acid (750 ml) and with brine (750 ml). The organic layer was concentrated under reduced pressure to a brown solid which was taken on to Example 7 without further purification. A sample of the solid was purified by granulation in ethyl acetate: methyl-tert-butyl ether (1:5, 4 ml/g).

¹H-NMR (300 MHz, CDCl₃): δ [ppm] 9.78(1H, s) 7.30 (5H, m), 6.15 (1H, br-d), 5.50 (1H, m), 3.05 (2H, m), 2.18 (3H, m), 2.00–1.55 (6H, m).

LRMS: m/z=295(M⁺)

Preparation 18

Benzyl (1S)-3-oxo-1-phenylpropylcarbamate



Sulphur trioxide pyridine complex (965 g, 6.1 mol) was slurried in dichloromethane (2 l) under an atmosphere of nitrogen. Dimethylsulfoxide (2 l) was added and the resultant solution was cooled to 0° C. A solution of benzyl (1S)-3-hydroxy-1-phenylpropylcarbamate (577 g, 2.0 mol), triethylamine (845 ml, 6.1 mol) and dimethylsulfoxide (1 l) in dichloromethane (1 ml) was added slowly to the reaction mixture keeping temperature below 10° C. The resultant yellow solution was stirred at 0° C. for 2.5 hours. A sample was analysed by TLC indicating that all starting material was consumed. Water (8.6 l) was added and a biphasic mixture was obtained. The mixture was diluted with toluene (8.6 l) and the layers were separated. The organic layer was concentrated under reduced pressure to yield a brown foam, which was taken on to Preparation 19 without further purification.

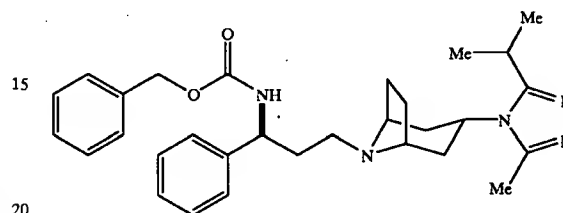
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¹H-NMR (300 MHz, CDCl₃): δ [ppm] 9.78(1H, s) 7.30 (5H, m), 6.15 (1H, br-d), 5.50 (1H, m), 3.05 (2H, m), 2.18 (3H, m), 2.00–1.55 (6H, m).

LRMS: m/z 283

Preparation 19

Benzyl (1S)-3-[3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropylcarbamate



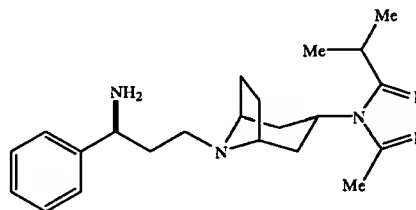
The title compound from Preparation 9 (13.5 g, 32 mmol) was slurried in dichloromethane (27 ml) and a solution of the compound from Preparation 18 (9.93 g, 35 mmol) in toluene (50 ml) and dichloromethane (50 ml) was added to the reaction mixture followed by addition of acetic acid (2.7 ml). To the resultant solution was added sodium triacetoxymethylborohydride (8.1 g, 38 mmol) in portions. The resultant slurry was stirred at ambient temperature for 1.5 hours. A sample was analysed by HPLC and TLC and the reaction was deemed complete. Water (27 ml) was added followed by 2 M aqueous sodium hydroxide solution (27 ml). The aqueous layer was basified to pH 11–12 by addition of 10 M aqueous sodium hydroxide and the layers were separated. The organic layer was washed with 1 M aqueous sodium hydroxide (27 ml) and with brine (27 ml). The organic layer was concentrated under reduced pressure to yield a pale brown foam, 13.3 g, 76%.

¹H-NMR (300 MHz, CDCl₃): δ [ppm] 1.39 (6H, d), 1.55–1.75 (4H, m), 1.84 (2H, m), 2.05 (2H, m), 2.15–2.45 (6H, m), 2.97 (1H, m), 3.36 (1H, br-s), 3.45 (1H, br-s), 4.25 (1H, m), 4.93 (1H, br-s) 5.10 (2H, m) 7.10–7.40 (10H, m).

LRMS: m/z 502

Preparation 20

(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenyl-1-propanamine



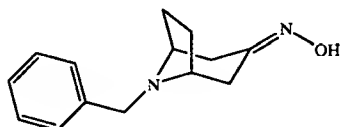
The title compound from Preparation 19 (309 g; 0.62 mol) was dissolved in methanol (3.1 l). Palladium (II) hydroxide (31 g) was added and the resultant slurry was stirred under an atmosphere of hydrogen at 345 kPa (50 psi) for 12 hours.

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A sample was taken and analysed by TLC and HPLC and the reaction was deemed complete. The reaction mixture was filtered through ArboceTM (filtration aid) and the filter pad was washed with methanol (500 ml). The methanolic solution was concentrated to afford the title compound as a white foam, 176 g, 78%. ¹H-NMR identical to the title compound from Preparation

Preparation 21

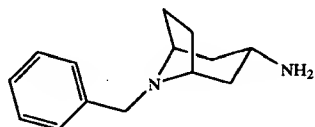
8-Benzyl-8-azabicyclo[3.2.1]octan-3-one oxime



A mixture of the title compound from Preparation 4 (50 g, 0.23 mol) was dissolved in industrial methylated spirit (250 ml). A solution of hydroxylamine hydrochloride (17.8 g, 0.26 mol) in water (250 ml) was added resulting in an exotherm. Sodium bicarbonate (23.4 g, 0.28 mol) was added and a small endotherm and frothing were noted. The resultant solution was stirred for 12 h. A white solid was formed and this was collected by filtration and dried in an oven under reduced pressure for 4 hours at 50° C. to give the title compound as a white solid, 43.1 g, 81% yield.

Preparation 22

Benzyl-8-azabicyclo[3.2.1]octan-3-exo-amine

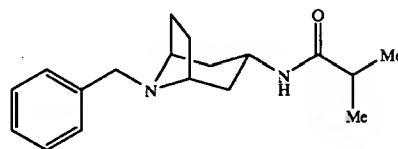


Clean sodium metal (24.3 g, 1.06 mol) was added in pieces to toluene (300 ml) at room temperature and the mixture was heated under reflux. A solution of the title compound from Preparation 5 (20.0 g, 87 mmol) in toluene (200 ml) and pentanol (120 ml) was added slowly over 15 minutes to the refluxing reaction. During this time gas evolution was observed. The resultant mixture was heated under reflux for 2 hours to ensure complete consumption of sodium. A thick white slurry had formed. The reaction was cooled to 80° C. and iso-propyl alcohol (200 ml) was added. The reaction was allowed to cool to room temperature and water (700 ml) was added. The aqueous layer was adjusted to pH 1 by the addition of concentrated hydrochloric acid (140 ml), (exotherm observed). The reaction was stirred for 15 minutes and the layers were separated. Ethyl acetate (700 ml) was added to the aqueous layer which was adjusted to pH 12 by the addition of 10 M aqueous sodium hydroxide (40 ml). The layers were separated and the organic layer was concentrated under reduced pressure to yield a pale yellow oil. Pentanol trapped in the oil was removed by azeotropic distillation with water (200 ml) and the water residue was removed by azeotropic distillation with toluene (200 ml) to give the title compound as a pale yellow oil containing traces of toluene, 18.0 g, 95% yield.

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Preparation 23

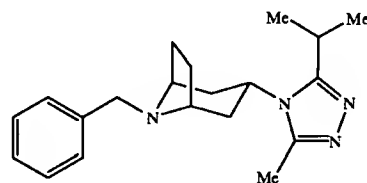
Exo-N-(8-benzyl-8-azabicyclo[3.2.1]oct-3-yl)-2-methylpropanamide



A 201 fixed rig was charged with dichloromethane (5 l), sodium carbonate (900 g), water (8.7 l) and the title compound from Preparation 6 (1200 g, 5.56 mol). The resultant mixture was cooled to 0° C. Isobutyryl chloride (700 ml, 6.67 mol) was added over 30 minutes keeping temperature below 10° C. The resultant mixture was stirred at from 0° C. to room temperature for 2 hours. The reaction was deemed complete after 2 hours by HPLC analysis. The layers were separated and the aqueous layer was washed with dichloromethane (1.5 l). The aqueous layer was pH 8. The combined organic layers were washed with 1 M aqueous sodium hydroxide solution (1.5 l) and the dichloromethane was distilled off and ethyl acetate added to give a final volume of 3 l. The resultant mixture was heated under reflux to give a clear brown solution. The solution was cooled to 25° C. over 1.5 hours and then to 2° C. over 1 hour and held at that temperature for 30 minutes. The white solid which had formed was separated by filtration and the filtrate was added to the reactor to mobilise the solid stuck on the bottom. The temperature was kept at 2° C. The resultant slurry was added to the filter cake. Ethyl acetate (0.6 l) was added to the reactor to retrieve the remaining solid and the slurry was added to the filter cake. The solid was dried in an oven under reduced pressure to give the title compound, 936 g, 59% yield. The liquors were evaporated under reduced pressure to a total volume of 1.5 l and the resultant brown solution 10 was cooled to 10° C. to give a slurry. The white solid was filtered off and dried in an oven under reduced pressure to give a second crop of title compound, 144 g, 9%. Overall yield: 1080 g, 68%.

Preparation 24

8-Benzyl-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]octane



A fixed rig was charged with dichloromethane (7 l) and PCl₅ (719 g, 3.45 mol).

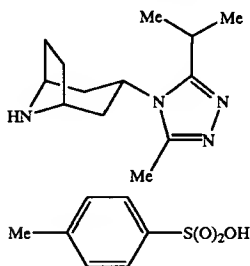
The resultant slurry was cooled to 0° C. A solution of the title compound from Preparation 7 (760 g, 2.66 mol) in dichloromethane (2.5 l) was added over 30 minutes keeping the temperature below 10° C. The resultant solution was stirred at from 0° C. to room temperature for 2 hours. The resultant pale yellow solution was cooled to 0° C. A solution of acetic hydrazide (315 g, 4.27 mol) in 2-methyl-2-butanol (ca. 1.5 l) (prepared by dissolving the acetic hydrazide in acetonitrile (1 l) and 2-methyl-2-butanol (2 l) and stripping off the acetonitrile and 500 ml of 2-methyl-2-butanol) was

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added slowly keeping temperature below 10° C. The resultant solution was stirred at room temperature for 15 hours. The reaction was deemed complete by HPLC analysis after 30 minutes but was held here for convenience. The mixture was cooled to 0° C. and 2 M aqueous sodium hydroxide solution (7.5 l) was added keeping temperature below 20° C. The aqueous layer was adjusted to pH 9 with 10 M aqueous sodium hydroxide solution (ca. 0.5 l). The layers were separated and the aqueous layer was washed with dichloromethane (1 l). The combined organic layers were evaporated under reduced pressure to give a 2-methyl-2-butanol concentrate (ca. 2.5 l). Ethyl acetate (1.5 l) and acetic acid (200 ml) were added. The resultant solution was heated to 80° C. for 30 minutes. The solution was cooled to room temperature overnight. The solution was cooled to 0° C. and the mixture was basified to pH 12 with 2 M aqueous sodium hydroxide solution (2 l). The layers were separated and the aqueous layer was washed with ethyl acetate (1 l). The combined organic layers were concentrated to ca. 2 l under reduced pressure and heptane (2 l) was added and the mixture evaporated in ca. 3 l under reduced pressure. Heptane (1.5 l) and ethyl acetate (300 ml) were added and the mixture was heated under reflux. The solution was cooled to 20° C. for 1 hour and to 0° C. for 2 hours. A white solid formed which was filtered off and dried in a vacuum oven under reduced pressure at 40° overnight to give the title compound, 622 g, 72% yield.

Preparation 25

3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]octane para-toluenesulfonic acid salt



The title compound from Preparation 8 (600 g, 1.85 mol) and para-toluenesulfonic acid monohydrate (351 g, 1.85 mol) were dissolved in methanol (3 l). 10% w/w Palladium-on-carbon (60 g) was added. The mixture was stirred under an atmosphere of hydrogen at 345 kPa (50 psi) and room temperature for 12 hours. A sample was taken and HPLC analysis showed that the reaction was complete. The reac-

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tion mixture was filtered through Arbocel™ (filtration aid) and the filter pad was washed with methanol (500 ml). The methanol was evaporated under reduced pressure and the resultant brown oil was dissolved in hot iso-propyl alcohol (1.8 l). The solution was allowed to granulate at room temperature for 12 hours and then at 0° C. for 2 hours. The white solid was filtered off and dried in a vacuum oven for 12 hours to give the title compound, 623 g, 83% yield.

Binlign activity

The compounds of Examples 1-5 were tested in the assay for CCR5 binding following the procedures disclosed in Combadiere et al, *J. Leukoc. Biol.* 60, 147-52 (1996) (mentioned above). All of the tested compounds were found to have an IC₅₀ value of less than 10 nM.

Appendix 1

PXRD Data on the Form A and Form B

Polymorphs Isolated From Examples 4 and 6

N-[(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-4,4-difluorocyclohexanecarboxamide, prepared by the methods of Examples 4 and 6, has been found to exist in 2 polymorphic forms termed Form A and Form B. The PXRD (Powder X-Ray Diffraction) pattern simulation involving d-spacing and relative intensities were calculated from single crystal structures using the Cerius² Diffraction-Crystal Module. The simulation parameters were:

Wavelength=1.54178 Å
Polarisation Factor=0.5
Crystallite Size=500×500×500 Å
Lorentzian Peak Shape

The main peaks (in degrees 2-theta) of the simulated PXRD patterns are listed in the following tables.

It will be appreciated by the skilled person that whilst the relative intensities of the various peaks in the tables may vary due to a number of factors including orientation effects of the crystals in the X-ray beam, the purity of the sample being examined or the degree of crystallinity of the sample, the peak positions will remain substantially as defined in the tables.

The skilled person will also appreciate that measurements taken using a different X-ray beam wavelength will result in different shifts in peak position according to the Bragg equation. Such PXRD patterns generated using different wavelengths are considered to be alternative representations of the PXRD patterns of the crystalline materials of the present invention and are thus to be embraced by the scope thereof.

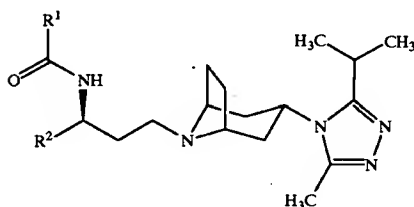
Angle 2-Theta	Intensity %	Angle 2-Theta	Intensity %	Angle 2-Theta	Intensity %	Angle 2-Theta	Intensity %
Peak Listings for Form A							
7.926	12.8	18.081	87.7	25.420	7.4	34.133	2.9
8.350	100.0	18.410	26.1	27.152	18.7	35.210	2.8
9.497	18.6	18.866	24.6	27.689	13.0	35.712	2.3
10.743	9.2	20.052	14.1	27.827	10.2	36.363	3.7
10.852	12.6	20.368	37.9	28.492	3.2	36.584	3.3
11.652	20.3	20.675	7.8	28.788	5.2	37.112	6.6
13.457	29.4	21.301	5.2	29.562	8.6	37.552	4.5
13.705	26.7	21.998	45.4	30.018	6.6	38.777	3.8
14.116	25.8	22.439	57.0	30.390	9.5	40.755	4.1

-continued

Angle 2-Theta	Intensity %	Angle 2-Theta	Intensity %	Angle 2-Theta	Intensity %	Angle 2-Theta	Intensity %
14.249	50.5	22.724	12.9	30.638	6.9	41.480	4.6
15.194	6.7	23.268	16.9	31.262	5.1	42.142	4.4
15.959	14.5	23.718	10.2	31.454	4.6	42.916	2.7
16.536	33.4	23.903	8.3	32.280	5.2	43.888	4.8
16.658	21.0	24.051	6.2	33.052	2.9	44.260	5.0
17.125	22.7	25.003	11.2	33.315	3.6	44.779	4.8
17.637	36.9	25.280	7.0	33.680	4.2		
Peak Listings for Form B							
7.622	1.4	20.712	13.1	29.009	9.6	36.634	8.0
9.561	5.0	21.697	8.5	29.588	3.2	36.986	4.0
9.992	43.3	22.406	23.8	30.137	6.6	37.635	2.9
11.194	47.6	23.037	27.3	30.373	6.3	38.255	4.5
11.528	24.0	23.138	27.5	30.726	9.2	38.442	4.8
12.619	47.9	23.826	4.4	31.338	8.9	39.064	5.1
14.156	44.8	23.983	4.1	31.824	14.2	39.391	3.4
15.052	51.2	24.484	5.3	32.351	4.5	39.792	3.9
15.28	27.0	24.691	6.4	33.105	2.4	40.540	2.1
16.041	64.8	25.181	10.3	33.470	2.5	40.985	6.5
16.371	40.6	25.358	8.7	33.685	2.5	42.126	3.7
17.070	36.1	25.928	10.6	34.032	6.7	42.397	4.3
17.360	78.0	26.390	7.2	34.447	2.5	42.983	2.5
18.046	66.6	26.696	13.2	35.131	9.0	43.328	3.4
18.946	23.9	27.301	3.5	35.643	3.9	44.219	3.6
19.202	16.1	27.864	5.1	35.812	4.0	44.690	5.5
20.088	100.0	28.498	10.8	36.239	4.0		

What is claimed is:

1. A compound of the formula:

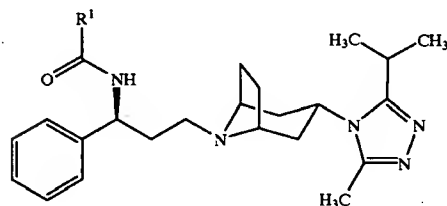


or a pharmaceutically acceptable salt or solvate thereof, wherein:

R¹ is C₃₋₆ cycloalkyl optionally substituted by one or more fluorine atoms, or C₁₋₆ alkyl optionally substituted by one or more fluorine atoms, or C₃₋₆ cycloalkylmethyl optionally ring-substituted by one or more fluorine atoms; and

R² is pbenyl optionally substituted by one or more fluorine atoms.

2. The compound of claim 1 of the formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

R¹ is either C₃₋₄ cycloalkyl optionally substituted by one or more fluorine atoms, or C₁₋₆ alkyl optionally substituted by one or more fluorine atoms.

3. The compound of claim 1, wherein R¹ is either C₄₋₆ cycloalkyl optionally substituted by one or two fluorine atoms, or C₁₋₄ alkyl optionally substituted by from one to three fluorine atoms.

4. The compound of claim 3, wherein R¹ is either cyclobutyl, cyclopentyl, 4,4-difluorocyclohexyl or 3,3,3-trifluoropropyl.

5. The compound of claim 1, wherein R² is pbenyl optionally substituted by 1 or 2 fluorine atoms.

6. The compound of claim 5, wherein R² is phenyl or monofluorophenyl.

7. The compound of claim 6, wherein R² is phenyl or 3-fluorophenyl.

8. The compound of claim 1 which is selected from the group consisting of:

N-[(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]cyclobutanecarboxamide;

N-[(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]cyclopentanecarboxamide;

N-[(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-4,4,4-trifluorobutanamide;

N-[(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-4,4-difluorocyclohexanecarboxamide; and

N-[(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl]-4,4-difluorocyclohexanecarboxamide;

or a pharmaceutically acceptable salt or solvate of any thereof.

9. A pharmaceutical composition comprising a compound of claim 1 and one of a pharmaceutically acceptable

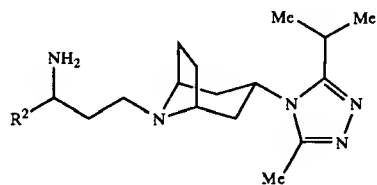
41

excipient, a pharmaceutically acceptable diluent or a pharmaceutically acceptable carrier.

10. A method of antagonizing a CCR5 receptor in a mammal comprising administering to said mammal in need thereof an effective amount of a compound of claim 1 to antagonize the CCR5 receptor-associated responses in said mammal.

11. A method of treating an inflammatory disease in a mammal comprising administering to said mammal an effective amount of a compound of claim 1.

12. A compound of the formula:

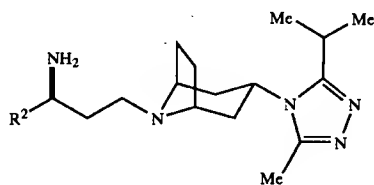


(IIA)

wherein R² is phenyl optionally substituted by one or more fluorine atoms.

13. The compound of claim 12, wherein R² is phenyl.

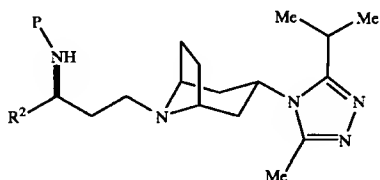
14. The compound of claim 12 of the formula:



(II)

15. The compound of claim 14, wherein R² is phenyl.

16. A compound of the formula:



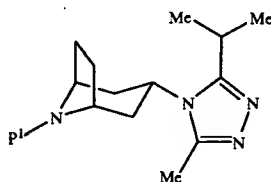
(VII)

wherein R² is phenyl optionally substituted by one or more fluorine atoms; and P is a protecting group.

17. The compound of claim 16, wherein R² is phenyl.

18. The compound of claim 16, wherein P is t-butyloxycarbonyl or benzyloxycarbonyl.

19. A compound of the formula:



(XII)

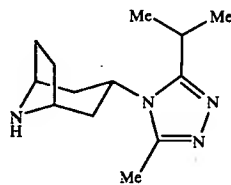
wherein P¹ is hydrogen or a protecting group.

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20. The compound of claim 19, wherein P¹ is benzyl.

21. The compound of claim 19, or a salt thereof, having the formula:

(VIA)



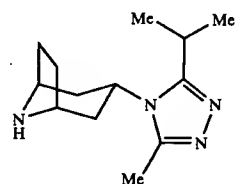
10

15

(VIA)

20

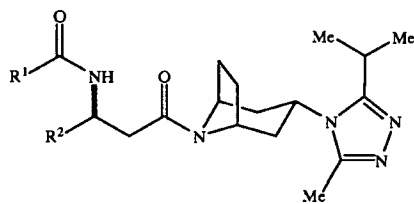
25



22. The p-toluenesulphonate salt of the compound of claim 21.

23. A compound of the formula:

(XIV)



35

40

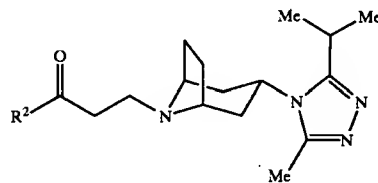
wherein R¹ is C₃₋₆ cycloalkyl optionally substituted by one or more fluorine atoms, or C₁₋₆ alkyl optionally substituted by one or more fluorine atoms, or C₃₋₆ cycloalkylmethyl optionally ring-substituted by one or more fluorine atoms; and

R² is phenyl optionally substituted by one or more fluorine atoms.

24. The compound of claim 23, wherein R² is phenyl.

25. A compound of the formula:

(XVIII)



60

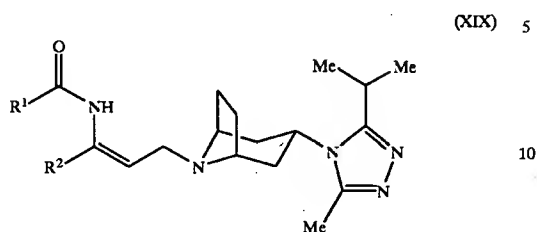
65

where R² is phenyl optionally substituted by one or more fluorine atoms.

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26. The compound of claim 25, wherein R² is phenyl.

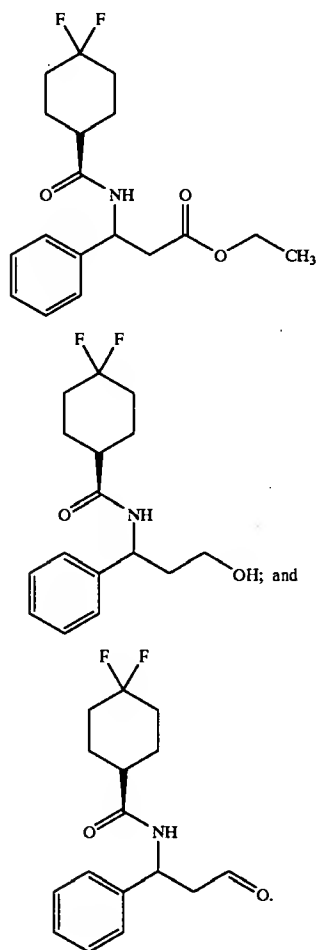
27. A compound of the formula:



wherein R¹ is C₃₋₆ cycloalkyl optionally substituted by one or more fluorine atoms, or C₁₋₆ alkyl optionally substituted by one or more fluorine atoms, or C₃₋₆ cycloalkylmethyl optionally ring-substituted by one or more fluorine atoms; and R² is phenyl optionally substituted by one or more fluorine atoms.

28. The compound of claim 27, wherein R² is phenyl.

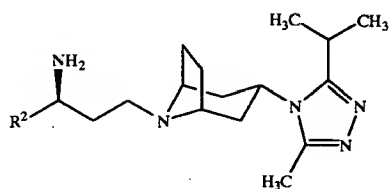
29. A compound selected from the group consisting of:



30. A process for the preparation of a compound of claim 1 selected from a process which comprises:

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(a) coupling a compound of the formula:



with a compound of formula:



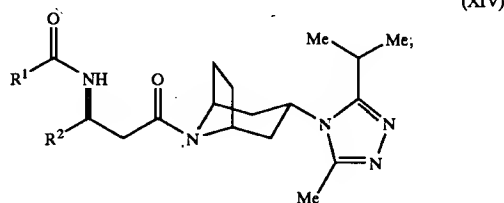
or

(b) reaction of a compound of the formula (II) with a compound of the formula:



where Z is a carboxylic acid activating, group; or

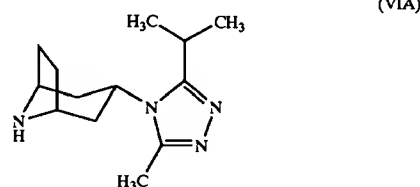
(c) reduction of a compound of the formula:



(d) reductive amination using a compound of the formula:



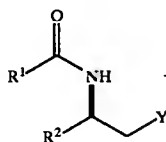
and a compound of the formula:



or a salt thereof; or

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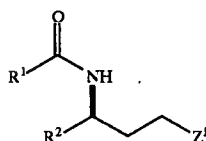
(e) reductive amination using a compound of the formula:



(XV)

where Y is CN, and a compound of the formula (VIA), or a salt thereof; or

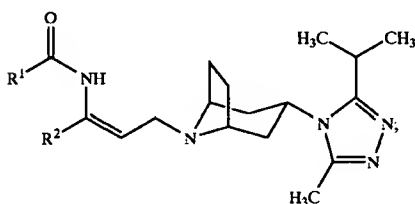
(f) alkylation of a compound of the formula (VIA), or a salt thereof, with a compound of the formula:



(XVII)

where Z¹ is a leaving group; or

(g) asymmetric reduction of a compound of the formula:



(XIX)

or

(h) reaction of a compound of the formula (II), or a metal salt thereof, with a compound of the formula:

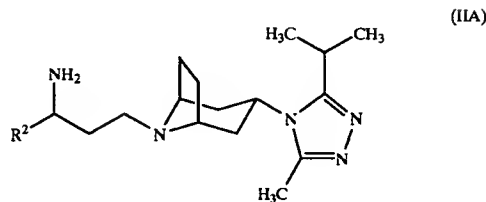


(XXIV)

where R⁵ is an ester forming group; or

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(i) reaction of a compound of the formula:



(IIA)

either with a compound of the formula (III) under coupling conditions, or a compound of the formula (VIB), and in the presence of a chiral catalyst:

wherein any one of processes (a) through (i) is optionally followed by conversion of a compound of claim 1 a pharmaceutically acceptable salt thereof.

31. A compound of claim 1 which is

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclobutanecarboxamide or a pharmaceutically acceptable salt or solvate thereof.

32. A compound of claim 1 which is

N-{(1S)-3-[3-(3-Isopropyl-3-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclopentanecarboxamide or a pharmaceutically acceptable salt or solvate thereof.

33. A compound of claim 1 which is

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-4,4,4-trifluorobutanamide or a pharmaceutically acceptable salt or solvate thereof.

34. A compound of claim 1 which is N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-4,4-difluorocyclohexanecarboxamide or a pharmaceutically acceptable salt or solvate thereof.

35. A compound of claim 1 which is

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl}-4,4-difluorocyclohexanecarboxamide or a pharmaceutically acceptable salt or solvate thereof.

* * * * *



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MAINTENANCE FEE STATEMENT

According to the records of the U.S. Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O. Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,667,314	\$900.00	\$0.00	05/17/07	09/865,950	12/23/03	05/25/01	04	NO	PC10925A

AA Documentum Electronic Signature Information

(Kapili Leilani)

06/10/03 13:09:34

Approval with Documentum password

**Pfizer Global Regulatory Affairs
Health Authority Contact**

Document ID: 101166

Product: UK-427,857 uk-427,857

Contact Date: 6/10/03

Category: IND 65,229

Country: USA

Initiated By: Pfizer ☒ Health Authority ☐ In Person ☐ Phone ☒ Fax ☐ E-Mail ☐

Health Authority Contact

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Title: Associate Director

Phone: 860.732.9967

Location: C2160

Drug Safety Related? ☐

Purpose:

FDA agreement on proposed amendment for A4001015, the IND opening study for UK-427,857 (CCR5 antagonist for HIV infection)

Summary:

During a June 3, 2003 teleconference, FDA requested centralized manual readings by a cardiologist and additional HR, BP, and ECGs on Day 5 of study A4001015 (see ROC 101156). A draft of the proposed protocol amendment was submitted on June 6, 2003. I spoke with Sean Belouin on June 9 to tell him the submission would be arriving and to request quick review to enable the amendment to be submitted to IRBs/ECs as soon as possible. He requested the relevant pages be faxed to him since he had not received his desk copy yet and he said he should be able to get a quick response from the reviewers.

I called on June 10 and Mr. Belouin said he was just going to call me. Dr. Murata (Medical Reviewer) and Dr. Laessig (Medical Team Leader) reviewed the amendment and considered the changes acceptable. I thanked Mr. Belouin for his help in getting the rapid review and told him the submission of the finalized amendment would be sent in today or tomorrow.

Pfizer Global Regulatory Affairs Health Authority Contact

Mr. Belouin also requested that submissions contain four copies for the IND (instead of the required triplicate) plus two desk copies to him. This ensures desk copies for any additional reviewers without him having to call for extra desk copies.

Abstract:

FDA requested protocol changes for the opening study for IND 65,229 (UK 427, 857) during June 3, 2003 teleconference. The proposed protocol amendment was submitted for review on June 6, 2003. FDA confirmed that the changes were acceptable on June 10, 2003.

Action:

Sites will submit June 6 version of the amendment to the IRBs/ECs for approval.

Inform SMS six copies should be submitted for IND submissions, including two desk copies to the FDA Project Manager.

CC:

Samantha Abel	James Baxter	Mohan Beltangady
Timothy Bertram	Marina Brodsky	Berkeley Cue
Claire Davies	Sandra Diroma	Robert Docherty
Michael Dunne	Felicia Feldman	Steve Felstead
Gordon Findlay	Hylar Friedman	Joseph Gaugas
Graham Higson	Chris Hitchcock	Joelle Ibanes
Anne Jenkins	Tim Jenkins	Diane Jorkasky
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John Sullivan	Mark Taisey	Larry Tremaine
Elna Van Der Ryst	RMOS, RIC/SRM AA WRA	Don Walker
Frederick Walker	Rob Webster	Ethan Weiner

**Pfizer Global Regulatory Affairs
Health Authority Contact**

Mike Westby

Chris Wiltshire

Jane Wood

Linked Document(s) :

None

Attachment(s) :

None

URL(s) :

None

Selzentry (maraviroc, UK-427,857) (CCR5-antagonist) for the treatment of HIV-1 infection IND-65,229& NDA 22-128

This chronology records all US regulatory activities from the initial IND submission date (May 06, 2003)

Color Legend:
Yellow - QT and ECG related correspondence
Pink - Hemodynamic related correspondence
Green - Visual related correspondence
Blue - Hepatotoxicity related correspondence
Purple - Malignancy related correspondence
Orange - Pancreatitis related correspondence

Date	Activity	Comments
2002-12-17	Submission to FDA	Pre-IND consultation information package
2003-02-03	FDA log	FDA fax to convey review comments regarding the pre-IND package
2003-02-25	Submission to FDA	Pfizer request for clarification on FDA pre-IND review comments
2003-02-25	FDA log	FDA fax to convey response to Pfizer's request for clarification
2003-03-06	Submission to FDA	Submit protocol A4001016 (thorough QT study) for review
2003-03-27	FDA log	FDA comments on Pfizer QT protocol
2003-05-06	Submission to FDA (0000)	Initial IND submission
2003-06-02	FDA log	FDA acknowledge receipt of IND
2003-06-04	FDA log	Minutes of June 3, 2003 teleconference with FDA regarding the safety review of the initial IND
2003-06-05	Submission to FDA (0001)	Pfizer meeting minutes of June 3, 2003 telecon with FDA regarding the safety review of the initial IND
2003-06-06	Submission to FDA (0002)	Request FDA review the amended protocol A4001015 which incorporated FDA's recommendations
2003-06-10	FDA log	FDA agreement on proposed amendment for A4001015
2003-06-11	Submission to FDA (0003)	Protocol amendment to A4001015
2003-07-08	FDA log	FDA convey initial IND review comments
2003-07-31	Submission to FDA (0004)	Request a meeting to discuss FDA's comments on clinical development plan and clinical pharmacology studies
2003-08-14	FDA log	Schedule teleconference on Oct 16, 2003 to discuss full development plan
2003-08-19	Submission to FDA (0005)	Submit toxicology study reports to FDA
2003-08-29	Submission to FDA (0006)	Submit clinical study report A4001005
2003-09-02	Submission to FDA (0007)	Submit new investigator information
2003-09-10	Submission to FDA (0008)	Submit pre-meeting package for October 16, 2003 telecon
2003-09-12	Submission to FDA (0009)	Notification of planned carcinogenicity dose selection proposal in rat
2003-10-03	Submission to FDA (0010)	Submit new investigator information
2003-10-03	Submission to FDA (0011)	Submit preliminary results of QT study A4001016
2003-10-08	Submission to FDA (0012)	Submit new protocol A4001018
2003-10-16	FDA log	Minutes of October 16, 2003 teleconference to discuss full development plan and drug interaction strategy
2003-10-21	Submission to FDA (0013)	Submit dose selection rationale for rat carcinogenicity study
2003-10-24	FDA log	FDA microbiology reviewer comments requesting that all subjects be genotyped at baseline with respect to the entire CCR5 coding region
2003-11-10	FDA log	FDA medical reviewer comments regarding Protocol A4001018
2003-11-11	Submission to FDA (0014)	Submit final reports for the drug metabolism studies
2003-11-21	Submission to FDA (0015)	Submit new investigator information
2003-11-21	Submission to FDA (0016)	Response to FDA request for information regarding FDA 11/10/03 fax
2003-11-25	Submission to FDA (0017)	Response to FDA request for information regarding FDA 10/24/03 fax
2003-12-04	FDA log	FDA response to Pfizer carcinogenicity special protocol assessment request-Final CAC Report
2003-12-09	Submission to FDA (0018)	Submit final toxicology study report
2003-12-09	FDA log	FDA microbiology reviewer comments concurring with Pfizer's 11/25/03 proposal
2003-12-23	Submission to FDA (0019)	Revised full development strategy
2004-01-13	Submission to FDA (0020)	Response to FDA CAC comments
2004-01-15	Submission to FDA (0021)	Request for end of Phase 2 meeting
2004-01-16	Submission to FDA (0022)	Response to FDA request for information regarding FDA 12/09/2003 fax
2004-02-02	FDA log	Teleconference with FDA to discuss the revised full development strategy
2004-02-05	Submission to FDA (0023)	Submit clinical study report for A4001008, A4001012 and A4001016
2004-02-16	FDA log	FDA scheduled type B meeting on March 31, 2004
2004-02-19	FDA log	FDA fax regarding doses for the rat carcinogenicity study
2004-02-24	FDA log	FDA fax with microbiology comments
2004-02-25	Submission to FDA (0024)	Submit pharmacology study reports to FDA
2004-03-10	FDA log	Pfizer request to reschedule the EoP2 meeting from March 14 to June 4, 2004
2004-03-16	Submission to FDA (0025)	Pfizer accept FDA's dose selection recommendations for the rat carcinogenicity study
2004-03-26	FDA log	FDA minutes of Feb 2, 2004 teleconference
2004-03-26	Submission to FDA (0026)	Pfizer comments on FDA Feb 2, 2004 meeting minutes

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2004-04-15 Submission to FDA (0027)	Submit new investigator information
2004-04-19 Submission to FDA (0028)	Submit outline of Tropism assay validation
2004-05-05 Submission to FDA (0029)	Request EoP2 CMC meeting
2004-05-06 Submission to FDA (0030)	Pre-meeting package of EoP2 meeting scheduled for June 4, 2004
2004-05-17 Submission to FDA (0031)	Information amendment for CMC
2004-05-21 FDA log	EoP2 CMC meeting scheduled July 16, 2004
2004-05-24 FDA log	Minutes of May 19, 2004 Scientific Advice meeting with Swedish MPA
2004-06-03 Submission to FDA (0032)	Submit final toxicology study report
2004-06-03 Submission to FDA (0033)	Pre-meeting package of EoP2 CMC meeting scheduled for July 6, 2004
2004-06-07 FDA log	Minutes of the June 7, 2004 clinical development meeting
2004-06-08 FDA log	Executive summary of June 7, 2004 clinical development meeting
2004-06-08 Submission to FDA (0034)	Response to FDA request for information regarding FDA 12/09/2003 fax
2004-06-10 CTA log	Minutes of June 10, 2004 Scientific Advice meeting with AFSSAPs, France agency
2004-06-22 Submission to FDA (0035)	Notification of planned carcinogenicity dose selection proposal in mouse
2004-06-23 Submission to FDA (0036)	Submit Pfizer minutes of June 7, 2004 clinical development meeting
2004-07-01 Submission to FDA (0037)	Submit final toxicology study report
2004-07-12 FDA log	Minutes of July 12, 2004 teleconference to follow up the issues from June 7, 2004 clinical development meeting
2004-07-16 Submission to FDA (0038)	Submit dose selection rationale for mouse carcinogenicity study
2004-07-16 Submission to FDA (0039)	Request for protocol review (A4001026, 1027, 1028 and 1029) along with revised clinical development plan
2004-07-19 Submission to FDA (0040)	Response to FDA request for information regarding request made at June 7 and July 12, 2004 meeting for datasets used in modeling/simulation studies
2004-07-20 Submission to FDA (0041)	Pfizer minutes of July 12, 2004 teleconference
2004-07-27 FDA log	Fax and email from FDA with comments regarding Pfizer's questions discussed during July 12, 2004 teleconference
2004-07-29 Submission to FDA (0042)	IND Annual Report
2004-07-29 Submission to FDA (0043)	Request for special protocol assessment regarding dose selection rationale for mice carcinogenicity study. Also request to withdrawal of Serial No.0038
2004-07-30 Submission to FDA (0044)	Submit clinical study report for A4001007 and A4001009
2004-08-02 FDA log	Reschedule the EoP2 CMC meeting to October 7, 2004
2004-08-04 Submission to FDA (0045)	Submit clinical study report for A4001011 and A4001013
2004-08-04 Submission to FDA (0046)	Submit clinical study report for A4001010
2004-08-05 Submission to FDA (0047)	Submit updated Investigator's Brochure (April 04)
2004-08-06 Submission to FDA (0048)	Response to FDA request for information regarding FDA July 27, 2004 fax
2004-08-11 FDA log	FDA comments regarding draft protocols submitted on July 16, 2004
2004-08-25 Submission to FDA (0049)	Submit revised protocols for study A4001026, 1027, 1028 and 1029
2004-09-01 FDA log	Receipt of FDA fax regarding dose selection proposal for mouse carcinogenicity study
2004-09-02 Submission to FDA (0050)	Addendum to April 2004 Investigator's Brochure
2004-09-03 Submission to FDA (0051)	Submit clinical study report for A4001015 and A4001018
2004-09-13 FDA log	FDA letter confirming EoP2 CMC meeting
2004-09-20 Submission to FDA (0052)	Submit clinical study report for A4001011 and A4001013
2004-09-21 FDA log	FDA comments regarding clinical study report for A4001011 and A4001013
2004-09-28 FDA log	FDA CMC review comments
2004-10-01 Submission to FDA (0053)	Response to FDA request for information regarding FDA September 28, 2004 comments
2004-10-07 FDA log	Executive summary and final Pfizer minutes for the EoP2 CMC meeting on October 7, 2004
2004-10-07 Submission to FDA (0054)	Update on drug interaction plan and preliminary analyses for A4001017, 1021, 1022 and 1025
2004-10-07 Submission to FDA (0055)	Request a teleconference
2004-10-20 FDA log	FDA fax with comments on the long-term follow up of treatment failures and format for the submission of tropism data
2004-10-22 Submission to FDA (0056)	Pfizer minutes of EoP2 CMC meeting
2004-11-01 Submission to FDA (0057)	Information amendment for CMC
2004-11-05 FDA log	FDA fax with statistical reviewer comments
2004-11-08 FDA log	Minutes of November 8, 2004 teleconference regarding statistical reviewer comments. The formal EoP2 will take place once Week 15 data are available from the naïve
2004-11-09 Submission to FDA (0058)	Response to FDA request for information regarding statistical reviewer comments
2004-11-22 Submission to FDA (0059)	Pfizer minutes of November 8, 2004 teleconference
2004-12-07 FDA log	Minutes of December 7, 2004 teleconference on the updated drug-drug interaction program
2004-12-10 Submission to FDA (0060)	Submit new investigator information
2004-12-10 Submission to FDA (0061)	Submit clinical study report for A4001017

2004-12-10	Submission to FDA (0062)	Submit toxicology study reports to FDA
2005-01-07	Submission to FDA (0063)	Inform FDA of MPA (Swedish agency) rejection of CTA for A4001026
2005-01-14	FDA log	Discussion with FDA Project Manager on the possibility of doing a small initial study in rheumatoid arthritis under the current IND
2005-01-14	Submission to FDA (0064)	Inform FDA Pfizer plan to submit the first monthly tropism reports on February 15, 2005. Same report will also be sent to AFSSAPS (French agency)
2005-02-01	Submission to FDA (0065)	Submit clinical study report for A4001022 and A4001025
2005-02-03	Submission to FDA (0068)	Inform FDA that maraviroc will be the recommended INN
2005-02-04	Submission to FDA (0067)	Pfizer letter to DSMB to inform visual adverse events in study A4001019. Also submit revised DSMB charter
2005-02-14	Submission to FDA (0068)	Submit clinical study report for study A4001019
2005-02-15	Submission to FDA (0069)	Submit clinical monthly report contain blinded efficacy and safety information
2005-02-23	Submission to FDA (0070)	Submit CMC related information including dissolution method development
2005-02-24: S. Br. case: 2: 1A (0071)		
2005-02-28	FDA log	Comments from clinical and microbiology reviewers
2005-03-03	Submission to FDA (0072)	Response to FDA February 28, 2005 comments regarding RLU data from study A4001029
2005-03-03	FDA fax	FDA fax with Clinical Pharmacology and Clinical comments
2005-03-04	FDA log	Report a death in study A4001027
2005-03-04	FDA log	Minutes of March 04, 2005 teleconference with FDA on possible protocol amendment to A4001026 in response to comments from some EU regulators
2005-03-07	Submission to FDA (0073)	Request a meeting to discuss the nature and content of studies of viral resistance to maraviroc
2005-03-08	Submission to FDA (0074)	Meeting minutes on discussion of Phase 2b/3 clinical program held between Pfizer, Spanish agency and Spanish patient advocate community
2005-03-08	Submission to FDA (0075)	Pfizer response to FDA comments regarding the proposed maraviroc dose when administered with saquinavir
2005-03-09	Submission to FDA (0076)	Submit minutes of March 04, 2005 teleconference
2005-03-14	Submission to FDA (0077)	Response to FDA request for information - provide ECG data for patient 10011008 in study A4001025
2005-03-18	Submission to FDA (0078)	Submit new investigator information
2005-03-18	Submission to FDA (0079)	Proposal for narratives to be written for clinical program
2005-03-21	Submission to FDA (0080)	Submit update on visual adverse events
2005-03-23	Submission to FDA (0081)	Submit toxicology study reports to FDA
2005-03-29	Submission to FDA (0082)	Process of submission of RLU data from study A4001029
2005-03-31	Submission to FDA (0083)	Submit monthly clinical report
2005-04-08	Submission to FDA (0084)	Submit status of native patient study A4001026
2005-04-11	FDA log	Pre-meeting package for May 10, 2005 teleconference to discuss virology plans to support Phase 2b/3 studies
2005-04-15	Submission to FDA (0085)	FDA response to Pfizer proposal regarding narratives for maraviroc
2005-04-19	Submission to FDA (0086)	Submit monthly clinical report
2005-04-22	Submission to FDA (0087)	Submit virology reports
2005-04-22	Submission to FDA (0088)	Request for fast track designation
2005-04-22	Submission to FDA (0089)	Submit new investigator information
2005-04-27	Submission to FDA (0090)	Response to FDA request for information on PK of boosted saquinavir
2005-04-28	Submission to FDA (0091)	Submit slides from ViroLogic for the May 10, 2005 teleconference
2005-05-02	FDA log	IND safety report (study 1027, PID 10660003, safety ref. 2005060012, acute renal failure, rash and hypotension)
2005-05-03	FDA log	FDA fax with comments from CMC reviewers on bracketing strategy
2005-05-05	Submission to FDA (0092)	FDA acknowledgement of request for fast track designation for maraviroc
2005-05-06	FDA log	Submit clinical study report for A4001020 and A4001021
2005-05-10	FDA log	FDA fax with CMC reviewer's comments on dissolution methods
2005-05-11	FDA log	Updated IND safety report on the renal failure case (PID 10660003, safety ref. 2005060012)
2005-05-16	Submission to FDA (0094)	Pfizer minutes of May 10, 2005 teleconference with FDA on the virology issues
2005-05-17	Submission to FDA (0095)	FDA email to clarify on their fax contains CMC reviewer's comments on dissolution methods from May 6, 2005
2005-05-17	FDA log	Updated IND safety report on the renal failure case (PID 10660003, safety ref. 2005060012)
2005-05-18	Submission to FDA (0096)	Submit Pfizer minutes of May 10, 2005 teleconference with FDA on virology issues
2005-05-18	Submission to FDA (0097)	Communication with FDA on a possible expedited safety report
2005-05-19	Submission to FDA (0098)	Submit monthly clinical report
2005-05-25	FDA log	Protocol amendment to A4001026, 1027 and 1028
2005-05-31	Submission to FDA (0099)	Submit CMC amendment
2005-06-07	Submission to FDA (0100)	Receipt of two FDA faxes with reviewer comments on analysis of AIDS-defining events and the probe saquinavir study
		Submit new protocol A4001046 (saquinavir study)
		FDA fax with medical reviewer's comments
		Submit new investigator information

2005-06-07 Submission to FDA (0101)	Submit poster presented at the XIV HIV drug resistance workshop
2005-06-09 FDA log	Request for emergency use of maraviroc in post-exposure prophylaxis
2005-06-09 FDA log	FDA granted Pfizer request for fast track designation for maraviroc
2005-06-09 FDA log	FDA minutes of May 10, 2005 teleconference on virology plans
2005-06-09 FDA log	FDA fax with clinical reviewer comments on study A4001046
2005-06-10 Submission to FDA (0102)	Response to FDA request for information on the dissolution method
2005-06-10 Submission to FDA (0103)	Response to FDA request for information on their May 31, 2005 fax which contained clinical queries
2005-06-16 Submission to FDA (0104)	Response to FDA request for information -single dose PK predictions with boosted saquinavir
2005-06-16 Submission to FDA (0105)	Submit updated Investigator's Brochure (June 2005)
2005-06-20 Submission to FDA (0106)	Submit monthly clinical report
2005-06-27 FDA log	FDA minutes of EoP2 CMC meeting
2005-06-28 Submission to FDA (0107)	Pfizer proposal for reporting unexpected and serious adverse event that are not related to drug
2005-06-28 Submission to FDA (0108)	Submit listing of tables to be provided to the DSMB
2005-06-30 Submission to FDA (0109)	Submit final protocol for A4001046
2005-07-08 Submission to FDA (0110)	Submit new investigator information
2005-07-11 FDA log	FDA agreed with Pfizer proposal to include the unexpected SAE considered not related to therapy in the monthly reports to FDA
2005-07-15 Submission to FDA (0111)	Submit monthly clinical report
2005-08-02 Submission to FDA (0112)	Submit IND safety reports for patient hospitalized for pneumonia (1027, PID 10370009, ref#2005090950) and for anemia (1027, PID 11060006, ref#2005103540)
2005-08-02 Submission to FDA (0113)	IND Annual Report
2005-08-03 Submission to FDA (0114)	Submit new investigator information
2005-08-10 FDA log	FDA query about plans for studying maraviroc in rheumatoid arthritis
2005-08-11 Submission to FDA (0115)	DSMB recommendations followed their July 22, 2005 meeting
2005-08-12 Submission to FDA (0116)	Protocol amendment for A4001029
2005-08-12 Submission to FDA (0117)	Submit IB Erratum
2005-08-17 Submission to FDA (0118)	Submit monthly clinical report
2005-08-26 Submission to FDA (0119)	Submit IND safety reports for patient developed aplastic anemia (1028, ref#2005117210) and syncopal episode (1026, ref#2005117093)
2005-08-31 Submission to FDA (0120)	Submit new investigator information
2005-09-08 Submission to FDA (0121)	Submit follow-up safety report for patient who developed anemia (1027, PID 11060006, ref#2005103540)
2005-09-13 Submission to FDA (0122)	Protocol amendment for A4001046
2005-09-15 Submission to FDA (0123)	Submit monthly clinical report
2005-09-19 Submission to FDA (0124)	Submit IND safety report for patient had right cerebral stroke, developed pneumonia and died (1027, ref#2005122260)
2005-09-22 Submission to FDA (0125)	Submit results of tipranavir interaction study
2005-09-23 Submission to FDA (0126)	Protocol amendment for A4001029 - to clarify the duration and procedures required after 48 weeks of therapy
2005-09-23 Submission to FDA (0127)	Submit virology proposal
2005-09-27 Submission to FDA (0128)	Submit follow-up safety report for patient who had right cerebral stroke, developed pneumonia and died (1027, ref#2005122260)
2005-09-30 Submission to FDA (0129)	FDA concurs with proposal for dissolution methodology
2005-10-03 FDA log	Submit new investigator information
2005-10-06 Submission to FDA (0130)	DSMB recommendations followed their September 28, 2005 meeting
2005-10-06 Submission to FDA (0131)	Submit overview of data on hepatic safety
2005-10-14 Submission to FDA (0132)	Submit monthly clinical report
2005-10-17 Submission to FDA (0133)	Submit IB Erratum
2005-10-20 Submission to FDA (0134)	FDA fax request for partially unblinded tables for maraviroc
2005-11-01 FDA log	Submit new investigator information
2005-11-02 Submission to FDA (0135)	Pfizer minutes of November 4, 2005 teleconference to discuss the required partially unblinded tables and to report a case of serious hepatotoxicity
2005-11-04 FDA log	Pfizer minutes of November 7, 2005 teleconference on the proposal for virology analyses for maraviroc and to provide update on recent SAEs
2005-11-07 FDA log	Submit report of hepatotoxicity for patient (PID 10650005, ref#2005149611)
2005-11-10 Submission to FDA (0136)	Submit report of hepatotoxicity for patient (PID 10650005, ref#2005149611)
2005-11-10 Submission to FDA (0137)	Submit Pfizer minutes of November 4, 2005 teleconference
2005-11-10 Submission to FDA (0138)	Submit Pfizer minutes of November 7, 2005 teleconference
2005-11-10 Submission to FDA (0139)	Update FDA on the case of hepatotoxicity and unexpected death in the maraviroc program
2005-11-11 Submission to FDA (0140)	Submit FDA requested information on median duration of therapy for maraviroc pivotal studies
2005-11-11 Submission to FDA (0141)	
2005-11-11 Submission to FDA (0142)	

2005-11-14	Submission to FDA (0143)	Covance submit partially unblinded tables to FDA. Pfizer submit 1571 only
2005-11-14	Submission to FDA (0144)	Submit IND safety report for patient had severe hepatotoxicity (1026, PID 10650005, ref#2005149611)
2005-11-15	Submission to FDA (0145)	Submit updated report of hepatotoxicity for patient (PID 10650005, ref#2005149611)
2005-11-15	Submission to FDA (0146)	Submit monthly clinical report
2005-11-15	Submission to FDA (0147)	Submit proposal for analysis of study A4001028
2005-11-16	Submission to FDA (0148)	Covance submit updated tables to FDA
2005-11-16	Submission to FDA (0149)	Submit IND safety report for patient who was diagnosed with a possible seizure (1027, PID 10520003, ref#2005151341)
2005-11-17	FDA log	FDA letter regarding information for the meeting being planned with the Forum for Collaborative HIV Research
2005-11-21	FDA log	Call to FDA regarding the planned open public meeting on long term safety of CCR5 antagonists
2005-11-23	Submission to FDA (0150)	Submit DSMB recommendations follow by their November 21, 2005 ad hoc meeting
2005-11-29	Submission to FDA (0151)	Submit new investigator information
2005-11-30	Submission to FDA (0152)	Submit Statistical analysis plans for A4001026, 1027, 1028 and 1029
2005-12-05	Submission to FDA (0153)	Submit follow-up safety report for patient who was hospitalized with pneumonia (1027, PID 10370009, ref#2005090950)
2005-12-06	Submission to FDA (0154)	Submit follow-up safety report for patient with hepatotoxicity (1026, PID 10650005, ref#2005149611)
2005-12-07	Submission to FDA (0155)	Submit IND safety report on patient diagnosed with G3 neutropenia (1026, PID 10860034, ref#2005160694)
2005-12-07	Submission to FDA (0156)	Submit Statistical analysis plan for the Analysis of virology data
2005-12-07	FDA log	FDA fax with response to Pfizer proposal for an interim analysis of the TE study in EU for maraviroc
2005-12-08	Submission to FDA (0157)	Submit updated safety information of patient 10820018 in study 1028 who died due to acute heart failure
2005-12-12	Submission to FDA (0158)	Submit Addendum to June 2005 IB
2005-12-15	Submission to FDA (0159)	Submit proposal for urgent review on survivability in the control and low-dose group at 90 weeks in the 2-year rat carcinogenicity study
2005-12-19	Submission to FDA (0160)	Submit proposal from Covance for partially unblinded tables. Pfizer only submit 1571
2005-12-20	Submission to FDA (0161)	Submit follow-up safety report for patient diagnosed with a possible seizure (1027, PID 10520003, ref#2005151341)
2005-12-21	Submission to FDA (0162)	Submit new investigator information
2005-12-20	FDA log	FDA fax request additional information for patient NER (1027, PID 10530008) and the incidence of hepatic enzyme abnormalities
2005-12-22	Submission to FDA (0163)	Submit FDA requested information for patient NER (1027, PID 10530008) and the incidence of hepatic enzyme abnormalities
2005-12-22	FDA log	Correspondence with FDA on survivability in rat carcinogenicity study for maraviroc
2005-12-30	Submission to FDA (0165)	Submit IND safety report for patient diagnosed with severe depression (1026, PID 10850002, ref#2005172554)
2005-12-30	Submission to FDA (0166)	Submit follow-up safety report for patient had hepatotoxicity (1026, PID 10650005, ref#2005149611)
2008-01-06	Submission to FDA (0164)	Submission from Covance for more partially unblinded data
2008-01-06	FDA log	FDA request for additional information on patient with liver-related adverse events
2006-01-06	FDA log	Correspondence with FDA about increasing the sample size in 1027 to allow for smaller number of patients in study 1028
2006-01-09	Submission to FDA (0167)	Covance submit the treatment assignment for 38 patients requested by FDA
2006-01-09	Submission to FDA (0168)	Submit FDA requested information on patients with liver-related adverse events in study 1026, 1028 and 1029
2006-01-10	FDA log	Inform FDA of DSMB recommendations followed their January 9, 2006 meeting
2006-01-10	Submission to FDA (0169)	Request for formal End of Phase 2 meeting
2006-01-12	Submission to FDA (0170)	Submit new investigator information
2006-01-12	Submission to FDA (0171)	Submit amendment for toxicology study
2006-01-18	Submission to FDA (0172)	Submission from Covance for partially unblinded tables. Pfizer only submit 1571
2006-01-18	Submission to FDA (0173)	Submit FDA requested information on patients with liver-related adverse events in study 1027
2006-01-18	Submission to FDA (0174)	Submit DSMB recommendations follow by their January 9, 2006 meeting
2006-01-19	Submission to FDA (0175)	Submit correspondence with FDA statistical reviewer about increasing sample size in study 1027
2006-01-19	Submission to FDA (0176)	Submit updated data on survivability in the rat carcinogenicity study
2006-01-20	Submission to FDA (0177)	Submit protocol amendment for study 1026 and 1027
2006-01-20	FDA log	Scheduling the formal EoP2 meeting for maraviroc
2006-01-20	FDA log	FDA fax with clinical reviewer comments for maraviroc
2006-01-26	Submission to FDA (0178)	Submit clinical study report for study A4001028
2006-01-23	FDA log	FDA agreed with Pfizer proposal to terminate the vehicle control and drug treated animals of that sex if survival falls below 20
2006-01-26	Submission to FDA (0179)	Submit protocol amendment for study 1028 and 1029
2006-01-30	Submission to FDA (0180)	Submit IND safety report for patient diagnosed with Stevens-Johnson syndrome (1026, PID 10650006, ref#2005172434)
2006-01-30	Submission to FDA (0181)	Submit CMC amendment
2006-01-31	Submission to FDA (0182)	Submit posters to be presented at CRO
2006-01-31	Submission to FDA (0183)	Submit response to FDA January 20, 2006 fax with clinical reviewer comments
2006-01-31	FDA log	FDA minutes for November 07, 2005 teleconference
2006-02-01	Submission to FDA (0184)	Submit new investigator information

2006-02-03	Submission to FDA (0185)	Withdrawal of serial No. 0179 and submit protocol amendment for study 1028 and 1029
2006-02-07	FDA log	FDA faxes with clinical pharmacology review comments and confirmation of the EoP2 meeting
2006-02-14	Submission to FDA (0186)	Submission from Covance for partially unblinded tables
2006-02-17	Submission to FDA (0187)	Submit new investigator information
2006-02-17	Submission to FDA (0188)	Submit DSMB recommendations to the restriction on the use of upranavir as part of the OBT. In studies 1027 and 1028.
2006-02-21	Submission to FDA (0189)	Submit protocol amendment for 1026
2006-02-23	FDA log	FDA comments on the statistical analysis plans for the phase 2b/3 studies
2006-03-02	Submission to FDA (0190)	Submit new report (A4001023) (Hepatic impairment)
2006-03-03	FDA log	Initial reviewer request information on all malignancies that have occurred during completed or ongoing MVC trials
2006-03-07	Submission to FDA (0191)	Minutes of telecon with FDA regarding statistical reviewer comments
2006-03-07	Submission to FDA (0192)	Response to FDA request for information: PK/PD data
2006-03-09	Submission to FDA (0193)	Protocol amendment for A4001027
2006-03-09	Submission to FDA (0194)	Submit new investigator information
2006-03-09	Submission to FDA (0195)	Pfizer minutes of 03 March 06 telecon with Statistical Reviewers
2006-03-14	Submission to FDA (0196)	Covance submit partially unblinded tables to FDA. Pfizer submit 1571 only
2006-03-16	Submission to FDA (0197)	Submit premeeting package for the formal EoP2 meeting
2006-03-17	Submission to FDA (0198)	Response to FDA request for information: summary of all malignancies
2006-03-17	Submission to FDA (0199)	Covance submit unblinded treatment assignment for 1028 and 1029 cases
2006-03-17	Submission to FDA (0200)	Response to FDA request for information: Topics for open public meeting scheduled for 31 May 2006
2006-03-17	Submission to FDA (to ONDC)	Request to participate in pilot program: submission of CMC information in a new drug application under the new Pharmaceutical Quality Assessment System
2006-03-20	Submission to FDA (0201)	Submit final toxicology study report of Study 2004-0091 (6-mo carci study in transgenic mice)
2006-03-27	CTA log	Meeting with French agency on 27 March 2006 to discuss hepatic safety.
2006-03-28	FDA log	The initial meeting with ONDC regarding participation in the CMC pilot program scheduled for 14 June 2006
2006-03-30	Submission to FDA (0202)	Submit updated DSMB Charter
2006-04-03	Submission to FDA (0203)	IND safety report (study 1028, PID 10180007, safety ref. 2006030716, myopathy, elevated CK)
2006-04-03	Submission to FDA (0204)	Submit new investigator information
2006-04-04	Submission to FDA (0205)	Letter to FDA to confirm DSMB role in recommending early discontinuation of a study as per FDA statistical reviewer request
2006-04-06	Submission to FDA (0206)	Submit clinical study report for A4001046 (boosted saquinavir study)
2006-04-11	Submission to FDA (0207)	Follow-up safety report for case 2006030716 (the events have been updated to myositis)
2006-04-11	FDA log	Executive summary of formal EoP2 meeting on 11 April 2006
2006-04-11	FDA log	Full minutes of formal EoP2 meeting on 11 April 2006
2006-04-13	Submission to FDA (0208)	Submission from Covance, only 1571 from Pfizer
2006-04-21	Submission to FDA (0209)	Submit case summary and lab results for patient 10880006 (study 1028) who had elevated transaminases
2006-04-25	Submission to FDA (0210)	Submit updated validation summary for tropism assay
2006-04-26	Submission to FDA (0211)	Submit Pfizer minutes of EoP2 meeting
2006-04-26	Submission to FDA (0212)	Submit follow-up safety report for case 2006030716 (correct blind breaking date)
2006-04-27	Submission to FDA (0213)	Submit new investigator information
2006-04-27	Submission to FDA (0214)	Submit DSMB 25 April 2006 recommendations
2006-05-08	Submission to FDA (0215)	Submit toxicology study amendments
2006-05-12	Submission to FDA (0216)	Submission from Covance
2006-05-16	Submission to FDA (0217)	IND safety report (study 1027, PID 10240002, safety ref. 2006030451, pancreatitis)
2006-05-16	FDA log	MAA Pre-submission meeting with Portuguese Infarmed held on 10 May 2006
2006-05-17	FDA log	MAA Pre-submission meeting with French Drug Agency (AFSSAPS) held on 13 May 2006
2006-05-18	Submission to FDA (0219)	Submit investigator information
2006-05-23	Submission to FDA (0220)	Submit follow-up safety report for case 2006030451
2006-05-23	Submission to FDA (0221)	Case summary for patient 10440012 in study 1028 who died on 15 May 2006 and the investigator reported the event as unrelated to the blinded study treatment
2006-05-24	FDA log	FDA minutes of EoP2 meeting
2006-05-30	Submission to FDA (0222)	Submit follow-up safety report for case 2006049231
2006-05-30	Submission to FDA (0223)	Submit pre-meeting package for 14 June 2006 meeting to discuss Pfizer's participation of the CMC pilot program
2006-06-02	Submission to FDA (0224)	Submit follow-up safety report for case 2006030716
2006-06-06	Submission to FDA (0225)	Submit proposed Trademark "CELSENTRI" for maraviroc
2006-06-08	Submission to FDA (0226)	Submit new investigator information

2006-06-12 Submission to FDA (0227)	Submit request for Deferral of Pediatric Data
2006-06-14 Submission to FDA (0228)	Submission from Covance
2006-06-14 Submission to FDA (0229)	Submit toxicology study report
2006-06-14 FDA log	Pfizer minutes of 14 June 2006 meeting to discuss inclusion of maraviroc into the CMC Pilot under the new Pharmaceutical Quality Assessment System
2006-06-15 Submission to FDA (0230)	Submit IND safety report (Study 1027, PID 11270012, safety ref: 2006071059, hypotension, dehydration, and to rule out sepsis)
2006-06-16 Submission to FDA (0231)	Submit IND safety report (Study 1026, PID 12030004, safety ref: 2006053529, attempt suicide)
2006-06-16 Submission to FDA (0232)	Submit IND safety report (Study 1027, PID 10630001, safety ref: 2006073815, central pontine myelinolysis)
2006-06-16 CTA log	MAA Pre-submission meeting with the Spanish Drug Agency (AEMPS) held on 14 June 2006
2006-06-20 CTA log	MAA Pre-submission meeting with the German Drug Agency (BfArM) held on 20 June 2006
2006-06-26 Submission to FDA (0233)	Submit follow-up IND safety report (Study 1026, PID 12030004, safety ref: 2006053529, attempt suicide)
2006-06-26 Submission to FDA (0234)	Submit follow-up IND safety report (Study 1027, PID 11270012, safety ref: 2006071059, hypotension, dehydration, and to rule out sepsis)
2006-06-26 Submission to FDA (0235)	Submit IND safety report (Study 1028, PID 11320002, safety ref: 2006030823, syncopal episode, bronchitis, pancytopenia)
2006-06-27 Submission to FDA (0236)	Submit follow-up IND safety report for patient diagnosed with severe depression (1026, PID 10650002, ref#2005172554)
2006-06-28 FDA log	FDA Office of New Drug Quality Assessment notify that maraviroc has been accepted to the CMC pilot under the Pharmaceutical Quality Assessment System
2006-06-30 Submission to FDA (0237)	Submit new investigator information
2006-06-30 Submission to FDA (0238)	Inform FDA of the proposed process of early partially unblinding of certain individual in order for Virology/pop PK analysis
2006-06-30 CTA log	MAA Pre-submission meeting with the UK Drug Agency (MHRA) held on 30 June 2006
2006-07-05 CTA log	MAA Pre-submission meeting with the Sweden Drug Agency (MPA) held on 29 June 2006
2006-07-08 Submission to FDA (0239)	Submit case summary and lab results for patient 12050011 (study 1026) who had lymphoma
2006-07-10 FDA log	FDA agreed with Pfizer proposal for a limited number of people to be unblinded early in order for the virology and PK analyses
2006-07-11 Submission to FDA (0240)	Submit follow-up IND safety reports for patient developed aplastic anemia (1028, PID# 11150001, ref#2005117210) and syncopal episode (1026, ref#2005117093)
2006-07-12 Submission to FDA (0241)	Submit PK datasets for study A4001026 (discontinued QD arm) and 1029
2006-07-13 Submission to FDA (0242)	Submission from Covance (Pfizer only submit 1571)
2006-07-14 FDA log	Formal letter from FDA of acceptance maraviroc into CMC pilot program
2006-07-17 Submission to FDA (0243)	Submit protocol amendment for study A4001029
2006-07-19 Submission to FDA (0244)	Submit follow-up IND safety report (Study 1028, PID 11320002, safety ref: 2006030823, syncopal episode, bronchitis, pancytopenia)
2006-07-24 Submission to FDA (0245)	Submit IND safety report (Study 1027, PID 10630001, safety ref: 2006073815, central pontine myelinolysis)
2006-07-25 Submission to FDA (0246)	Submit proposal for maraviroc electronic CTD
2006-07-26 Submission to FDA (0247)	Response to FDA request for information: Review of Category C events and Long Term Follow up
2006-07-31 Submission to FDA (0248)	Submit follow-up IND safety report for patient diagnosed with Stevens-Johnson syndrome (1026, PID#10650006, ref#2005172434)
2006-08-01 Submission to FDA (0249)	Submission from Covance (Pfizer only submit 1571)
2006-08-01 Submission to FDA (0250)	Submit investigator information
2006-08-03 Submission to FDA (0251)	Submit IND Annual Report (09 March 2005 to 06 March 2006)
2006-08-07 FDA log	FDA response on Pfizer proposal for long-term follow-up of patients in studies with maraviroc
2006-08-08 Submission to FDA (0252)	Submit all Pharm/tox study report on CD
2006-08-08 FDA log	FDA reviewer request for information regarding the expanded access program, the inclusion of patient profiles in the NDA, and a request from DMETS for the review (ref#2005122260)
2006-08-08 Submission to FDA (0253)	Submit follow-up IND safety report for patient had right cerebral stroke, developed pneumonia and died (1027, PID# 10310007 ref#2005122260)
2006-08-11 Submission to FDA (0254)	Submit protocol outline and protocol synopsis for the expanded access program
2006-08-15 Submission to FDA (0255)	Submit D SMB 09 August 2006 recommendations
2006-08-15 Submission to FDA (0256)	Request for CMC pilot meeting
2006-08-17 FDA log	Schedule of second meeting on the CMC pilot program
2006-08-22 Submission to FDA (0257)	Submit new protocol A4001052 (TMC114 interaction study)
2006-08-23 Submission to FDA (0258)	Submit final tables for study A4001029 and proposed table shells for SCS and SCE
2006-08-24 FDA log	FDA agree to the proposed changes to the tables to be submitted after initial filing
2006-08-28 Submission to FDA (0259)	Submit new investigator information
2006-08-31 FDA log	Schedule pre-NDA meeting on November 28, 2006
2006-08-31 FDA log	FDA agreed to refer to discussion at the EoP2 meeting to indicate the deferral of the start of the pediatric studies
2006-09-01 FDA log	FDA letter confirm that the 2nd CMC pilot meeting (Quality by Design) to be scheduled on Oct 19, 2006
2006-09-05 Submission to FDA (0260)	Submit follow-up IND safety report (Study 1028, PID 11320002, safety ref: 2006030823, syncopal episode, bronchitis, pancytopenia)
2006-09-13 Submission to FDA (0261)	Request for pre-NDA meeting
2006-09-14 Submission to FDA (0262)	Submission from Covance
2006-09-22 Submission to FDA (0263)	Submit new investigator information
2006-09-27 FDA log	IND number assigned for the planned treatment IND for maraviroc
2006-09-28 FDA log	Minutes of the MAA pre-submission meeting with EMEA

2008-09-29	FDA log	Acceptance of the proposed tradename for maraviroc - Celsentri
2008-10-03	Submission to FDA (0264)	Submit A4001029 clinical study report (wk 24)
2008-10-04	Submission to FDA (0265)	Submit pre-meeting package for the CMC pilot meeting scheduled on 19 Oct 2006
2008-10-05	FDA log	FDA letter confirm that the pre-NDA meeting on Nov 28, 2006
2008-10-10	Submission to FDA (0266)	Submit IND safety report (Study 1028, PID 11130001, safety ref: 2006118394, thrombosis and chest pain)
2008-10-11	Submission to FDA (0267)	Submit follow-up IND safety reports for patient developed aplastic anemia (1028, PID# 11150001, ref#2005117210)
2008-10-16	Submission to FDA (0268)	Submit updated IB (October 2006)
2008-10-19	Submission to FDA (0269)	Submit investigator information
2008-10-19	FDA log	Minutes of CMC pilot meeting held October 19, 2006
2008-10-23	Submission to FDA (0270)	Submit follow-up IND safety report (Study 1028, PID 11130001, safety ref: 2006118394, thrombosis and chest pain)
2008-10-25	FDA log	Assignment of NDA number and agree on the Highlights section of the label does not need to be coded for the initial submission
2008-10-30	Submission to FDA (0271)	Submit October 19 2006 CMC pilot program meeting minutes
2008-10-31	Submission to FDA (0272)	Submit pre-NDA meeting briefing package
2008-11-02	Submission to FDA (0273)	Submission from Covance
2008-11-08	Submission to FDA (0274)	Submit request for rolling review of NDA
2008-11-13	Submission to FDA (0275)	Agreement to submit CMC sections P.2 and S.2.6 to start the rolling submission of the MVC NDA
2008-11-13	Submission to FDA (0276)	Protocol Amendment - Revised FDA 1572 Forms
2008-11-21	CMC submission to FDA (0001)	Submit Toxicology 03012 3-Month oral dose-range-finding study in mice
2008-11-28	FDA Log	Submit CMC section P2 and S.2.6 of module for NDA to start rolling submission of MVC NDA
2008-11-30	FDA Log	Executive summary of PreNDA Meeting for maraviroc.
2008-12-05	Submission to FDA (0277)	FDA fax with microbiology comments
2008-12-05	FDA Log	Submit IND Safety Report (Study 1028 Safety ref: 2006145805 (cholangiosarcoma))
2008-12-05	FDA log	Written Request for pediatric studies
2008-12-06	Submission to FDA (0278)	FDA minutes of CMC meeting 19 October 2006
2008-12-07	FDA log	Response to FDA request for information: Virology Data sets
2008-12-08	FDA log	Issue Final full minutes of Pre-NDA Meeting for Maraviroc
2008-12-08	Submission to FDA (0279)	Teleconference with FDA to discuss expanded access program
2008-12-08	Submission to FDA (0280)	Protocol Amendment 1572 forms
2008-12-11	Submission to FDA (0281)	Follow up IND Safety report Study 1028 Safety ref: 2006145805 (cholangiosarcoma)
2008-12-11	Submission to FDA (0282)	Submit 28 November 2006 Full minutes of Pre-NDA Meeting
2008-12-12	Submission to FDA (0283)	Response to FDA handling of unblinded patients in 1027 1028
2008-12-13	Submission to FDA (0284)	Protocol 1059 filed
2008-12-19	Submission to FDA (0000)	IND Safety Report, PID 1026 11040004, safety ref: 2006150277
2008-12-19	FDA Log	NDA 22-128 FILED
2008-12-20	Submission to FDA (0002)	IND acknowledgement letter for Treatment IND 76,169
2008-12-21	Submission to FDA (0285)	NDA 22-128 Certification of Filing to NDA
2008-12-21	Submission to FDA (0286)	IND Safety Report Follow up: PID 1028 11430002, safety ref: 2006145805
2008-12-21	Submission to FDA (0287)	CMC Information
2008-12-22	Submission to FDA (0003)	FDA Request for Information: SAE and Cat C events for patients on Open Label Maraviroc
2007-01-05	Submission to FDA (0288)	NDA 22-128 Response to FDA Request for SCP Module 2.7.2 in QBR format
2007-01-05	Submission to FDA (0289)	Submission from Covance
2007-01-09	FDA Log	Protocol Amendment 1572 forms
2007-01-09	Submission to FDA (0290/0003)	Tentative date for AC meeting for NDA 24 April 2007
2007-01-10	FDA log	Information amendment Investigators' Brochure Addendum
2007-01-10	FDA log	Formal notification of AC meeting 24 April 2007
2007-01-10	FDA Log	Receipt of Safe to Proceed letter for Expanded Access Program IND 76,169
2007-01-11	Submission to FDA (0291/0004)	IND Safety Report, PID 1028 11430002, safety reference: 2006145805 (cholangiosarcoma)
2007-01-11	Submission to FDA (0292)	New Protocol A4001041 DI Study of etravine; etravine darunavir ritonavir
2007-01-16	Submission to FDA (0004)	NDA 22-128 Response to FDA Request for additional narratives list sent
2008-01-17	Submission to FDA (0005)	NDA 22-128 Response to FDA Request for narratives - narratives supplied for SAE and Cat C events on CD ROM
2007-01-17	FDA log	IND Safety Report, PID 1026 11040004, safety ref: 2006150277, 1028 11430002 (cholangiosarcoma)
2007-01-23	Submission to FDA (0006)	FDA response to proposal for adolescents and expedited safety reporting for expanded access IND
2007-01-24	Submission to FDA (0007)	IND 76,169 Information Amendment Clinical Protocol A4001050 Comments to FDA on adolescents and safety reports for malignancies and SAEs
2007-01-24	Submission to FDA (0007)	IND 76,169 Information Amendment Clinical Protocol A4001050 amendment

2007-01-26 Submission to FDA (0234/0000) IND Safety Report PID 1028 11430002 safety reference 2006145605 (choleangiosarcoma/Death)

2007-01-29 Submission to FDA (0006)
NDA 22-128 Response to FDA request for information Clinical
Minutes of 29 Jan 2007 telecon with Microbiology reviewers
2007-01-29 FDA Log
NDA 22-128 Response to FDA request for information - Pharmacology Toxicology
2007-01-29 Submission to FDA (0007)
Protocol amendment for A4001041 1572 forms
2007-02-02 Submission to FDA (0295)
NDA 22-128 Proposal to submit gp160 sequence data
2007-02-05 Submission to FDA (0008)
NDA 22-128 Response to FDA request for information onset of AE's in safetyd ata sets
2007-02-07 Submission to FDA (0010)
Response to FDA request for information
2007-02-08 FDA Log
Queries received from FDA Stats reviewers
2007-02-08 FDA log
Queries from Division of Scientific Investigations DSI
2007-02-09 FDA Log
Receipt of NDA Filing letter for Maraviroc
2007-02-09 FDA log
Comments on EAP protocol
2007-02-12 Submission to FDA (0296)
Covance submission (Pfizer 1571 form and covance 1572 forms)
2007-02-13 Submission to FDA (0012)
NDA 22-128 Repose to FDA request for information Statistics
02/13 2007 Submission to FDA (0297)
Cross reference authorization for Gilead Protocol GS-US-183-0018
2007-02-15 Submission to FDA (no#)
NDA 22-128 Study site information requested by DSI (no sequence number)
2007-02-15 Submission to FDA (0013)
Study Site information requested by DSI
2007-02-16 FDA log
Queries from pharmacometric and microbiology reviewers
2007-02-16 FDA Log
FDA Minutes of Pre-NDA meeting
2007-02-16 Submission to FDA (0014)
NDA 22-128 gp160 sequence data

2007-02-19 Submission to FDA (0233/0000) IND Safety Report PID 1028 10510000 Ref 2007030542 Hepatic failure, schizophrenia

2007-02-19 FDA log
FDA request for SAS programs to recreate study report tables
2007-02-19 Submission to FDA (0016)
NDA 22-128 Response to FDA request for information
2007-02-20 Submission to FDA (0011)
NDA 22-128 Pharmacology Toxicology study report 911/092 (out of sequence)
2007-02-20 Submission to FDA (0010)
IND 76,169 protocol amendment resubmit AppB for A4001050
2007-02-21 Submission to FDA (0015)
NDA 22-128 Updates to e-CTD
2007-02-21 Submission to FDA (0017)
NDA 22-128 gp160 sequence data
2007-02-22 Submission to FDA (0299)
FDA Minutes of Pre-NDA meeting
2007-02-22 Submission to FDA (0019)
NDA 22-128 FDA minutes of pre-NDA meeting
2007-02-23 Submission to FDA (0018)
NDA 22-128 Response to FDA request for information PK/PPD data sets
2007-02-27 Submission to FDA (0020)
NDA 22-128 Response to FDA - Microbiology comments
2007-02-27 FDA Log
Comments from Microbiology Reviewers for Maraviroc
2007-02-27 Submission to FDA (0300)
Info amend CMC 12 m data
2007-02-27 Submission to FDA (0022)
NDA 22-128 Microbiology Study Report D/I 154/06
2007-02-28 Submission to FDA (0021)
NDA 22-128 Repose to FDA request for information on PK/PPD datasets
2007-03-01 Submission to FDA (0021)
NDA 22-128 Request to submit data on X4 patients who failed therapy
2007-03-01 FDA log
FDA request for full population PK datasets for Maraviroc
2007-03-01 FDA Log
FDA request for QT-exposure dataset for Maraviroc
2007-03-05 Submission to FDA (0023)
NDA 22-128 Response to FDA request for QT exposure analysis
2007-03-07 Submission to FDA (0011)
IND 76,169 New Investigators and 1572
2007-03-07 Submission to FDA (0301)
1572 forms
2007-03-07 Submission to FDA (0024)
NDA 22-128 Advisory Committee Meeting Briefing document
2007-03-08 FDA log
Minutes of teleconference with FDA Stats and Medical reviewers
2007-03-09 Submission to FDA (0302/0012) Initial IND Safety Report PID 1028 10330001 Ref 2007014899 Proteinuria
2007-03-12 Submission to FDA (0025) NDA 22-128 Narratives on Serious Adverse Events
2007-03-12 Submission to FDA (0027)
NDA 22-128 Response to FDA request for information Patient Weights
2007-03-13 Submission to FDA (0028)
NDA 22-128 Response to FDA request for AE datasets
2007-03-13 FDA log
Scheduling of pre-approval inspections of the manufacturing sites for maraviroc
2007-03-16 Submission to FDA (0303)
New protocol A4001060 Study of tropism assay
2007-03-16 FDA log
NDA 22-128 Follow up on request for drug interaction table
2007-03-19 FDA log
NDA 22-128 Correspondence regarding the highlights section of the USPI
2007-03-19 FDA log
Follow up on request for failed patients with X4 virus in 1027/28
2007-03-20 Submission to FDA (0029)
NDA 22-128 Pfizer meeting minutes with FDA Statistical Reviewers
2007-03-20 submission to FDA (0030)
NDA 22-128 3-month safety update

2007-03-20 Submission to FDA (0031)	NDA 22-128 Response to FDA request for information SAS logs
2007-03-20 Submission to FDA (0032)	NDA 22-128 Response to FDA request for information PK/PD data sets
2007-03-21 FDA Log	Request for Cmin calc and exposure response analyses
2007-03-22 Submission to FDA (0304)	1571 only letter from Covance
2007-03-22 Submission to FDA (0037)	NDA 22-128 final briefing document without redaction
2007-03-22 Submission to FDA (0034)	NDA 22-128 final CSR A4001029 with datasets
2007-03-22 FDA Log	NDA 22-128 Additional information for inspections of manufacturing sites
2007-03-22 submission to FDA (0036)	NDA 22-128 Pop PK and exposure responses
2007-03-23 Submission to FDA (0038)	NDA 22-128 Cini Pharm Drug interaction Table
2007-03-23 Submission to FDA (0039)	NDA 22-128 TLOVR time to loss of virologic response
2007-03-29 FDA Log	Request for duration of obs DBTx and Post Tx
2007-03-29 FDA Log	Info request from CMC reviewers
2007-03-30 FDA Log	comments from Clin Pharm reviewers on Cmin and exposure response analyses and slides for FDA AC
2007-04-02 FDA Log	Receipt of formats for USPI
2007-04-02 FDA Log	Request for further Cmin and exposure response telecon
2007-04-02 Submission to FDA (0026)	NDA 22-128 Response to FDA request for information Microbiology
2007-04-04 Submission to FDA (0040)	TLOVR datasets in response to FDA request
2007-04-05 FDA Log	Telcon with FDA Clin Pharm re Cim and exposure response clarification
2007-04-05 FDA log	receipt of FDA briefing package
2007-04-05 Submission to FDA (0041)	Exposure response and pop PK analyses
2007-04-06 Submission to FDA (0305)	1572 forms
2007-04-06 Submission to FDA (0042)	Clini Pharm response on Cmin, FDA slides comments
2007-04-08 Submission to FDA (0043)	Response to FDA Information on Immune Markers and CROI poster
2007-04-09 Submission to FDA (0044)	Patient Narratives
2007-04-09 Submission to FDA (0306/0014)	IND Safety report SIR #2007025960 PID 1028 10860004 fractured olecranon
2007-04-12 FDA Log	Discussion of errata to FDA BP
2007-04-12 Submission to FDA (0046)	DSMB safety report
1905-06-29 Submission to FDA (0307)	DSMB recommendations
2007-04-19 Submission to FDA (0045)	CMC information
2007-04-20 FDA Log	Request for Narratives on patients with Rhabdomyositis
2007-04-27 Submission to FDA (0049)	Advisory committee slides
2007/04-30 Submission to FDA (0053)	Revision to SPL version of proposed USPI
2007-04-30 FDA Log	Fax from FDA on comments on discussion points from FDA AC 24 April 2007
2007-05-01 FDA Log	Responses to recent clinical comments from FDA on QT studydata sets of viral load
2007-05-02 FDA Log	discuss submitting promotional materials to DDMAC
2007-05-03 FDA Log	Request for postmarketing commitments
2007-05-03 Submission to FDA (0308)	Protocol amendment
2007-05-03 Submission to FDA (0309)	Protocol amendment new portocol A4001066
2007-05-04 Submission to FDA (0047)	Spilus codes for OCS stats information viral load and CD4 measurements already submitted
2007-05-04 Submission to FDA (0050)	response to request for information A4001002 datasets
2007-05-04 Submission to FDA (0052)	response to request for information QT study A4001016
2007-05-07 FDA Log	Request for Isoniazid use in studies and in EAP
2007-05-10 FDA log	Request for Post marketing and CMC request
2007-05-10 Submission to FDA (0055)	Clinical comments submission 30 April
2007-05-10 Submission to FDA (0057)	Summary of post marketing commitments
2006-05-11 Submission to FDA (0056)	Narratives on Lymphomas
2007-05-11 FDA log	email letter objections to Tradename CELSENTRI
2007-05-11 FDA log	FDA query on liver function tests in patients who took isoniazid
2007-05-14 FDA LOG	FDA query on proposed dosing adjustment for patients with renal failure and estimated Cmax for MVR take with efavirenz or nevirapien w.o. protease inhibitor
2007-05-14 Submission to FDA (0310)	Follow-up SIR report#2007025960 PID 102810860004 Fractured right olecranon
2007-05-15 FDA Log	FDA letter on objections to tradename
2007-05-15 Submission to FDA (0311)	Submission from Covance
2007-05-16 Submission to FDA (0058)	Response to FDA use of isoniazid and if allowed in EPA
2007-05-16 Submission to FDA (0059)	response to FDA data to support dosing ajustment in renal impairment who take CYP3A inhibitors

2007.05.16 FDA Log	request to rmodelling data in patients with renal failure
2007.05.17 Submission to FDA (0060)	TRADENAME
2007.05.22 Submission to FDA (0062)	Response to DMETS evaluation of tradename
2007.05.22 Submission to FDA (0312)	Follow-up SIR#2007006542PID 102810510038 Hepatic failure, schizophrenia
2007.05.23 Submission to FDA (0313)	Initial SIR#2007037504 PID 102911110002 Gastric Lymphoma
2007.05.24 Submission to FDA (0061)	Toxicology report amendment
2007.05.24 Submission to FDA (0063)	Patient Narrative gastric lymphoma 102911110002
2007.05.24 Submission to FDA (0064)	Response to request for Clin Pharm information
2007.05.24 Submission to FDA (0065)	Response to request for Clin Pharm information
2007.05.24 FDA Log	FDA proposed postmarketing commitments for maraviroc
2007.05.24 FDA Log	FDA request for CMC reviewers
2007.05.25 FDA Log	FDA comments on USPI for maraviroc
2007.05.25 Submission to FDA (0314)	Protocol amendment: new investigator
2007.05.29 Submission to FDA (0315)	Follow-up SIR#2007025960 PID 102810860004 Fractured right olecranon
2007.05.30 Submission to FDA (0316)	Initial SIR#2006108056 PID 102710520002 Esophageal cancer
2007.05.31 Submission to FDA (0317)	Pfizer acceptance of Pediatric Written Request and proposes a staged approach to the studies
2007.06.01 Submission to FDA (0066)	Response to FDA request for information-CMC
2007.06.01 FDA log	FDA fax with proposed Clinical Pharmacology postmarketing commitments
2007.06.04 Submission to FDA (0067)	Response to FDA comments on the Proposed USPI
2007.06.05 Submission to FDA (0068)	Proposed postmarketing commitments
2007.06.05 Submission to FDA (0318)	Follow-up SIR#2006108056 PID 102710520002 Esophageal cancer & Follow-up SIR#2007037504 PID 102911110002 Gastric Lymphoma
2007.06.08 FDA Log	Query from clinical pharmacology team leader for maraviroc on a finding from the inspection of the Singapore Phase 1 unit
2007.06.08 FDA Log	Teleconference with CMC reviewers
2007.06.11 Submission to FDA (0319)	Follow-up SIR#2007037504 PID 102911110002 Non-Hodgkin's Lymphoma
2007.06.12 Submission to FDA (0069)	Response to FDA request for information-Clinical Pharmacology, Response to Proposed Clin Pharm postmarketing commitments
2007.06.14 Submission to FDA (0070)	Response to FDA request for information-CMC
2007.06.14 Submission to FDA (0071)	Initial reports of SAE-A4001066
2007.06.14 Submission to FDA (0320)	Initial report of SAE from study A4001066- a healthy female subject developed rash, fever, eosinophilia and elevated LFT
2007.06.18 Submission to FDA (0321)	Follow-up SIR#2006108056 PID 102710520002 Esophageal cancer
2007.06.18 FDA Log	Discussion and agreement on a postmarketing epidemiology study to follow patients for safety endpoints
2007.06.19 Submission to FDA (0072)	Response to FDA request for information-Clinical reread of ECGs from study A4001016
2007.06.19 Submission to FDA (0322)	Submission from Covance
2007.06.19 Submission to FDA (0323)	Protocol amendment: change in protocol A4001060
2007.06.20 FDA Log	Receive of approvable letter for maraviroc
2007.06.21 Submission to FDA (0073)	Additional information on subject 34, A4001066
2007.06.21 Submission to FDA (0324)	Protocol amendment: revised FDA 1572 forms
2007.06.22 Submission to FDA (0074)	Response to FDA 20 June 2007 Action Letter
2007.06.25 FDA Log	Discussions regarding the proposed postmarketing commitments
2007.07.06 Submission to FDA (0075)	Update on Patient 34, Study A4001066
2007.07.10 Submission to FDA (0076)	A4001026 Week 48 Top Line Report
2007.07.12 Submission to FDA (0077)	?
2007.07.12 Submission to FDA (0325)	Follow-up SIR#2007043580 PID 102810050007 Hemoptysis, respiratory arrest, anemia, etc.
2007.07.17 FDA Log	Minutes of telecon with FDA on 17 July 2007 on additional data submitted since receipt of the approvable letter and the path forward to approval of the maraviroc NDA
2007.07.20 Submission to FDA (0326)	Protocol amendment: new investigator: revised FDA 1572 forms
2007.07.24 Submission to FDA (0327)	Follow-up SIR#2007055940 PID 102810050007 Pneumonia, respiratory arrest
2007.07.25 Submission to FDA (0078)	Resubmission-Response to Approvable letter
2007.08.03 Submission to FDA (0328)	Submit IND Annual Report (09 March 2006 to 08 March 2007)
2007.08.06 Submission to FDA (0079)	Final USPI and Medication Guide
2007.08.06 FDA Log	Receipt of the approval letter for Seizentry (maraviroc) from FDA
2007.08.07 FDA Log	Correction to the postmarketing commitment study requirement regarding pharmacokinetics in patients with renal impairment
2007.08.08 FDA Log	Receipt of fax correcting one of the postapproval commitments listed in the approval letter for Seizentry
2007.08.10 FDA Log	Teleconference with FDA regarding the surrogate marker study A4001060
2007.08.13 Submission to FDA (0329)	Letter of cross-reference: Division of Acquired Immunodeficiency Syndrome Study A5241
2007.08.13 Submission to FDA (0080)	SPL for approved NDA 22-128

2007.08.13 Submission to FDA (0081)
2007.08.16 Submission to FDA (0330)
2007.08.20 Submission to FDA (0331)

Letter of Cross-Reference
Protocol Amendment: Revised FDA 1572 forms
Follow-up SIR# 2007064690 PID 102711060001 Cardiac Arrest and Death